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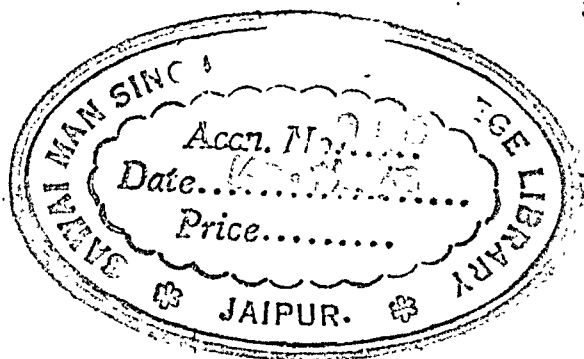
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ANTECEDENT JAUNDICE IN CIRRHOSIS OF THE LIVER

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AND

CECIL JAMES WATSON, M.D.

MINNEAPOLIS

THE ETIOLOGY of cirrhosis of the liver has not been fully elucidated. In a certain small percentage of cases the disease is dependent on exposure to hepatotoxic agents, such as arsenic, cinchophen, carbon tetrachloride and other chemicals. In a larger percentage, varying with the type of population studied, the condition is associated with chronic alcoholism. In these cases it may be that diets deficient in protein initiate the development of fatty liver and eventual transition to cirrhosis,¹ in accord with results of experimentation on animals.² This subject has been reviewed recently by György^{2c} and need not be considered further at present. In addition to the cases of cirrhosis of the liver associated with chronic alcoholism, there remains, however, a fairly large group of cases not readily classified. The question has been raised in the past as to whether infectious hepatitis (infectious jaundice; acute catarrhal jaundice) may be an important factor in the pathogenesis of cirrhosis in a certain proportion of cases. This relationship has been affirmed by some and denied by others. F. B. Mallory, in his classification of cirrhosis, described the so-called toxic cirrhosis or healed acute yellow atrophy, which is characterized by a small liver with large, irregular lobulations separated by contrasting but non-

From the Department of Medicine, Medical School, University of Minnesota Hospital Minneapolis.

1. Connor, C. L.: Fatty Infiltration of the Liver and the Development of Cirrhosis in Diabetics and Chronic Alcoholism, *Am. J. Path.* **14**:347-363 (May) 1938.

2. (a) Lillie, R. D.; Daft, F. S., and Sebrell, W. H.: Cirrhosis of Liver in Rats on Deficient Diet and Effect of Alcohol, *Pub. Health Rep.* **56**:1255-1258 (June) 1941. (b) Webster, G. T.: Cirrhosis of the Liver Among Rats Receiving Diets Poor in Protein and Rich in Fat, *J. Clin. Investigation* **21**:385-392 (July) 1942. (c) György, P.: Experimental Hepatic Injury, *Am. J. Clin. Path.* **14**:67-88 (Feb.) 1944.

proliferative connective tissue.³ This form resembles the *hepar lobatum* of an old syphilitic condition and differs fundamentally from a diffuse cirrhosis of the so-called portal, or Laennec, type. Additional examples of "healed acute yellow atrophy" or "toxic cirrhosis" representing the end result of infectious hepatitis have been described by Bergstrand,⁴ More recently, Lucké,⁵ in discussing the pathologic changes in cases of fatal hepatitis, figured typical examples of the "*hepar lobatum*" of so-called toxic cirrhosis, although he did not use the term cirrhosis in discussing them. In any event, the condition is comparatively rare and accounts for but relatively few of the cases presenting the clinical picture of hepatic cirrhosis.

One is impressed by the lack of definite criteria in the literature relating to "toxic cirrhosis" and "healed acute yellow atrophy." Thus Pratt and Stengel⁶ described 5 cases of "toxic cirrhosis" only 2 of which had a history of previous jaundice, and in both of these instances the illness today would undoubtedly be called infectious hepatitis rather than acute yellow atrophy. Furthermore, the pathologic descriptions indicated the presence of a diffuse cirrhosis rather than of an irregularly nodular "toxic cirrhosis" in Mallory's sense. It is probable that these cases represent instances of diffuse portal cirrhosis developing as a sequel to infectious hepatitis. Jones and Minot⁷ studied 26 cases of infectious hepatitis (catarrhal jaundice) with courses varying from less than two weeks to six months. In 5 of these the condition progressed to undoubted portal cirrhosis, with confirmation at autopsy in 2 instances. It was their opinion that this relationship had not been fully appreciated. Soffer and Paulson,⁸ using the bilirubin tolerance test, found evidence of residual hepatic functional impairment in 9 of 11 patients with infectious hepatitis, 8 of whom had been in the acute stage of the disease from three to eighteen years previously. They expressed the opinion that in a certain unspecified proportion of cases of infectious hepatitis the disease runs a progressive course,

3. Mallory, F. B.: Cirrhosis of the Liver: Five Different Types of Lesions from Which it May Arise, *Bull. Johns Hopkins Hosp.* **22**:69-75, 1911.

4. Bergstrand, H.: *Ueber die akute und chronische gelbe Leberatrophie*, Leipzig, Georg Thieme, 1930.

5. Lucké, B.: The Pathology of Fatal Epidemic Hepatitis, *Am. J. Path.* **20**: 471-593 (May) 1944.

6. Pratt, J. H., and Stengel, A.: Toxic Cirrhosis Resulting from Acute Liver Atrophy, *Am. J. M. Sc.* **173**:1-11 (Jan. 28) 1927.

7. Jones, C., and Minot, G. R.: Infectious (Catarrhal) Jaundice: An Attempt to Establish a Clinical Entity, *Boston M. & S. J.* **189**:531-551 (Oct. 18) 1923.

8. Soffer, L. J., and Paulson, M.: Residual Hepatic Damage in Catarrhal Jaundice as Determined by the Bilirubin Excretion Test, *Arch. Int. Med.* **53**:809-813 (June) 1934.

ultimately leading to portal cirrhosis. Lucké,⁹ on the other hand, having examined at autopsy (death being due to unrelated causes) or biopsy specimens during the convalescent period in 14 cases of hepatitis at varying intervals from the acute attack, expressed doubt that such a relationship exists. The number of cases in Lucké's study is, of course, much too small to permit any conclusion in this regard. It is worthy of note that in the large series of fatal cases of subacute atrophy of the liver which Bergstrand observed in epidemic form in Sweden in 1927 there were the following distinct types of cirrhosis: *hepar lobatum* (corresponding with the toxic cirrhosis of Mallory); diffuse, coarsely granular Laennec cirrhosis, and diffuse, finely granular Laennec cirrhosis.⁴ Eppinger¹⁰ suggested that many of the cases of what Bergstrand termed subacute atrophy were of what would now usually be classified as "icterus catarrhalis," in other words, what has come to be referred to generally as infectious hepatitis. This simply emphasizes the relationship between infectious hepatitis and acute or subacute atrophy of the liver, and there seems to be general agreement that the only difference is one of degree of severity.

Relatively few statistical studies have been carried out on the incidence of previous jaundice in cirrhosis of the liver. Of Bloomfield's 41 patients, 36 of whom were alcoholic patients, 4, or approximately 10 per cent, had had a previous episode of jaundice.¹¹ Of the 386 patients with cirrhosis collected by Ratnoff and Patek,¹² but 25, or 6.5 per cent, had had previous episodes of jaundice, and no attempt was made in their study to define the type of jaundice experienced. Two hundred and seven, or 54 per cent, of their cases were associated with chronic alcoholism, and it may be assumed that a fatty liver and hence an intermediate fatty cirrhosis was the usual sequence of events in the development of the portal or atrophic cirrhosis which was observed. Eppinger¹³ stated that 14 per cent of 269 males and 12 per cent of 107 females suffering with cirrhosis had a previous history of "catarrhal jaundice." In the same material the incidence of alcoholism was 52 and 19 per cent respectively.

The occurrence of large numbers of cases of infectious hepatitis during the war which has just ended, especially among members of

9. Lucké, B.: The Structure of the Liver After Recovery from Epidemic Hepatitis, *Am. J. Path.* **20**:595-619 (May) 1944.

10. Eppinger, H.: *Die Leberkrankheiten*, Berlin, Julius Springer, 1937.

11. Bloomfield, A. L.: The Natural History of Chronic Hepatitis (Cirrhosis of the Liver), *Am. J. M. Sc.* **195**:429-444 (April) 1938.

12. Ratnoff, O. D., and Patek, A. J.: The Natural History of Laennec's Cirrhosis of the Liver: An Analysis of Three Hundred and Eighty-Six Cases, *Medicine* **21**:207-268 (Sept.) 1942.

13. Eppinger, H.: Zur Klinik der Leberzirrhose, *Verhandl. d. Gesellsch. f. Verdauungs. u. Stoffwechselkr.* **5**:251-269, 1925.

the armed services, together with an experience with a number of cases in which there was evident progression of infectious hepatitis to cirrhosis, has stimulated our interest in the question of incidence of antecedent jaundice in cirrhosis of the liver. The purpose of the present study was to obtain further information on this point, with particular reference to the cases of cirrhosis at the University of Minnesota Hospital as observed during the past ten years.

MATERIAL AND METHODS

The case records of all patients with cirrhosis admitted to the inpatient services of the University of Minnesota Hospital in the past ten years were analyzed with special regard to previous episodes of jaundice. During the period 1935 to 1944 inclusive, records were available on 100 patients with a diagnosis of cirrhosis of the liver. In 30 of the cases the diagnosis was proved by biopsy of the liver or at autopsy. Fifty-two of the remainder were clearcut cases of cirrhosis clinically and on the basis of laboratory studies. In the remaining 18 the diagnosis was somewhat doubtful, for the following reasons: 1. In 5 cases an obstructive biliary cirrhosis on the basis of a "silent" calculus was not definitely excluded. 2. In 5 cases the laboratory findings were not entirely typical. Numerous tests of hepatic functions, some of them no longer used, have been employed in the University Hospital during this ten year period. It is beyond the scope of this paper to discuss the validity of the various tests. Suffice it to say that since 1940, at least, the sulfobromophthalein retention test and the Takata-Ara test, or more recently, the cephalin-cholesterol flocculation test have been carried out in almost all the cases of cirrhosis. In all cases in which these tests were made, one or more tests showed an abnormal reaction. 3. In 3 cases positive results of serologic tests of the blood suggested the possibility of syphilitic hepatic damage. 4. In 5 cases the diagnosis of cirrhosis was doubtful for miscellaneous reasons. It was our impression, after careful study of the records, that at least 10 of these 18 cases did in fact represent instances of cirrhosis.

The control series consisted of 100 patients with miscellaneous disorders excluding hepatic disease of any type. This group corresponded to the group with cirrhosis so far as sex distribution, age (in the same decade of life) and year of last admission to the hospital were concerned.

The establishment of a previous episode of jaundice as definitely representing infectious hepatitis was difficult in many cases. It was believed that if an attack of jaundice had occurred several years before the onset of the patient's present illness and had been associated with jaundice in members of the patient's family or other persons in the neighborhood, it almost certainly represented infectious hepatitis.

In addition, when a previous attack of jaundice had the following characteristics, the history was considered to be highly suggestive of infectious hepatitis: (1) jaundice preceded by or accompanied with anorexia, nausea and, usually, vomiting; (2) lack of pain or at most a vague distress in the right upper quadrant of the abdomen or epigastrium; (3) spontaneous clearing. Further, if an episode of spontaneously clearing jaundice occurred in the patient's youth, i. e., before the age of 20, it was considered to be indicative of infectious hepatitis even if no further details were given. Weil's disease, which might offer confusion in this regard, is extremely rare in Minnesota.

The criteria for alcoholism are admittedly inexact. Few case records mentioned specific amounts of alcohol ingested; therefore, statements to the effect

that patients had severe or moderate alcoholism were taken at face value. Possibly a few cases of alcoholism were missed, but it is our experience that a history of alcoholism, if present, may usually be obtained from relatives or friends if not from the patient.

RESULTS

Of the 100 patients with cirrhosis, 67 (67 per cent) were men and 33 (33 per cent) were women. Twenty-three of the men and 2 of the women, a total of 25 (25 per cent), were classified as having severe alcoholism.

Thirty-three of the 100 patients (33 per cent) had been jaundiced at some time previously (table 1). Seventeen of these (17 per cent of the total) gave histories strongly suggestive of an episode of infectious hepatitis in the past. Two of these 17 persons also had severe alcoholism. Three patients in addition may have had infectious hepatitis

TABLE 1.—*Antecedent Jaundice in Cirrhosis of the Liver*

A. 100 cases of cirrhosis of the liver

1. 33 patients (33%) had a history of previous jaundice. 17 (17%) had clearcut infectious hepatitis
2. 36 patients (36%) had definitely had no jaundice in the past
3. 50 patients (50%) had records which did not indicate whether or not there had been jaundice in the past

B. Control group—100 cases of miscellaneous disorders

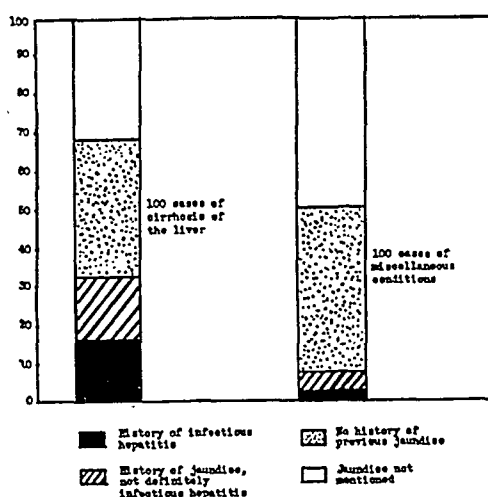
1. 7 patients (7%) had a history of previous jaundice. 3 (3%) had had possible attacks of hepatitis
 2. 43 patients (43%) had definitely had no jaundice in the past
 3. 50 patients (50%) had records which did not indicate whether or not there had been jaundice in the past
-

in the past. One of these had had jaundice thirty years previously, with no further details given. In this case the diagnosis of cirrhosis was not definite, the main problem being the presence of anemia which did not respond to any form of therapy, and the patient was considered to have latent cirrhosis. The second was a 3 year old boy who had been jaundiced from the age of 6 weeks to that of 5 months and then free of symptoms until he was 2½ years old, at which time characteristic symptoms and signs of cirrhosis developed. Biopsy of the liver revealed typical cirrhosis. The third patient had had a ten day bout of jaundice ten years previously, coincident with the use of iodine therapy for hyperthyroidism. The remaining 13 patients had had previous jaundice which was probably not infectious hepatitis. Seven of these, including 3 alcoholic patients, had had intermittent jaundice for one to nine years previous to their admission to the hospital, most probably accounted for by the onset of cirrhosis at that time. Three others were patients with ulcerative colitis, which may well have been related to the development of cirrhosis. Of the 3 remaining patients with previous

jaundice, there was a question of hemolytic anemia in 1, another had had gallstones and in the third a primary carcinoma of the liver was found at autopsy, with "scarring of the remainder of the liver." Whether this indicated an underlying cirrhosis was not clear from the protocol.

Of the 67 males in the cirrhotic group, in whom the incidence of alcoholism was 34 per cent, 20, or 30 per cent of the group, had a history of previous jaundice, and 8, or 12 per cent, had probably had hepatitis in the past. On the other hand, in the 33 women, only 2 (6 per cent) of whom had alcoholism, 13, or 40 per cent of the group, had been jaundiced previously, and 9, or 27 per cent, had probably had hepatitis in the past.

Thirty-six (26 per cent) of the whole group gave no history of jaundice previous to the onset of the present complaint. Ten of these had severe alcoholism. The records of the remaining 31 patients (31



Antecedent jaundice in cirrhosis of the liver.

per cent) failed to indicate whether jaundice had or had not been present at any time in the past. Nine of these were patients with severe alcoholism.

In the control series of 100 patients with miscellaneous disorders, only 7 (7 per cent) had had jaundice at some time previous to their admission to the hospital. Forty-three (43 per cent) gave a history of no jaundice at any time, while the records of the remaining 50 (50 per cent) failed to indicate whether jaundice had or had not occurred in the past. Of the 7 patients who had had jaundice previously, only 3 (3 per cent of the total) gave histories suggestive of episodes of infectious hepatitis.

In figure 1, in which the percentages for the two series are compared, it is seen that the figures are based on the entire group of 100 patients in each instance, including those whose records failed to con-

tain a statement as to previous jaundice. If these are eliminated from both series, it is found that 33 (48 per cent) of 69 patients in the cirrhotic group and 7 (14 per cent) of 50 patients in the control group had had jaundice previously. The probability that such a difference would arise through chance alone is less than 1 in 10,000.¹⁴ In terms of histories of probable hepatitis the figures are: 17 (23 per cent) of 69 cases in the cirrhotic group compared with 3 (6 per cent) of the control series of 50 cases. The statistical probability is similarly less than 1 in 10,000 that chance alone might account for the difference.

Of 75 patients with no history of alcoholism, 27 (36 per cent) had had jaundice previous to the onset of the present complaint. Fifteen of these (20 per cent) had histories strongly suggestive of hepatitis previously, while an additional 3 (4 per cent) had had possible hepatitis in the past. As noted in the foregoing, but 2 of the 25 alcoholic patients in the series gave a history suggestive of hepatitis.

TABLE 2.—*Antecedent Jaundice in Cirrhosis of the Liver Proved by Autopsy or Biopsy*

30 cases
14 patients (47%) had a history of previous jaundice
7 (23%) had had clearcut infectious hepatitis
7 (23%) had definitely had no jaundice
9 (30%) had records which did not indicate whether or not there had been jaundice in the past

Of the 30 patients who had a diagnosis of cirrhosis proved at autopsy or biopsy (table 2), in 14 (46 per cent) the symptoms were highly suggestive of infectious hepatitis, 7 (23 per cent) had had no jaundice in the past, and no definite statement was made in the records of the remaining 9 (31 per cent). It will be seen that the correspondence between these figures and those for the group as a whole is close, especially when the comparatively small size of the former group is considered.

Eighteen cases were mentioned previously in which, for various reasons, the diagnosis of cirrhosis of the liver was somewhat doubtful. Two of these were cases in which a previous episode of hepatitis seemed likely. Of the 82 patients, then, for whom the diagnosis of cirrhosis was established with reasonable certainty, at least 15, or 18 per cent, had probably had hepatitis in the past. When the doubtful cases were excluded, the percentage of cases with a history of probable hepatitis is seen to be slightly higher than in the entire group.

14. Prof. Alan Treloar, Division of Biostatistics, University of Minnesota, supplied us with this analysis.

COMMENT

Watson and Hoffbauer¹⁵ have described in detail the case of a 48 year old woman, one of the instances included in the present series of cases of cirrhosis. This patient had had a definite attack of infectious hepatitis in 1912, at the age of 15. She remained intermittently jaundiced for the ensuing thirty years, presenting the clinical picture of Hanot's cirrhosis, i. e., chronic jaundice, pruritus and hepatosplenomegaly without ascites. Death occurred following a large hemorrhage from an esophageal varix. A biopsy of the liver performed in 1936 revealed pronounced chronic hepatitis with early cirrhosis. Another biopsy of the liver in 1945 showed a considerably more advanced cirrhosis, a finding borne out at autopsy in the same year. This is perhaps the most striking instance yet recorded in which infectious hepatitis has gradually undergone transition to cirrhosis of the liver.

Watson and Hoffbauer emphasized that the cirrhosis following hepatitis is of the relatively nonfatty type, in contradistinction to the typically fatty cirrhoses of chronic alcoholism and food deficiency. The

TABLE 3.—*Alcoholism Versus Antecedent Jaundice in Cirrhosis of the Liver*

Ratnoff and Patek, 386 cases	{	Alcoholism, 54%
	{	Antecedent jaundice, 6.5%
Eppinger, 376 cases	{	Alcoholism, 42%
	{	Antecedent jaundice, 13%
Present series, 100 cases	{	Alcoholism, 22%
	{	Antecedent jaundice, 33%

cirrhosis occurring after hepatitis is at times of "cholangiolitic" type, that is to say, exhibiting definite evidence of cholangiolar functional derangement.¹⁵ In 5 of the present group of 14 cases the disease was of this type. One additional instance of the same type, believed to represent a transition from hepatitis to cirrhosis, has been studied in another hospital. Three cases, not included in the series reported on here, have been studied recently in which the evidences of cholangiolar regurgitation of bile¹⁵ were lacking. Thus, our experience to date embraces 6 cases of cholangiolitic or so-called Hanot type plus 15 of the ordinary portal type, a total of 21 in which there was an antecedent history indicative of infectious hepatitis.^{15a} Of the 15 cases, several

15. Watson, C. J., and Hoffbauer, F. W.: The Problem of Prolonged Hepatitis with Particular Reference to the Cholangiolitic Type and to the Development of Cholangiolitic Cirrhosis of the Liver, *Ann. Int. Med.* **25**:195-227, 1946.

15a. Since this was written, several additional cases have been studied which are likewise believed to represent a transition from hepatitis to cirrhosis. These include another case very similar to that of the 48 year old patient mentioned here; again, an initial attack of epidemic hepatitis was followed by a chronic disease characterized by jaundice of varying intensity, pruritus, hepatosplenomegaly and chemical evidence of cholangiolar regurgitation.

exhibited minor evidences indicative of cholangiolar involvement, such as a moderate increase of promptly reacting serum bilirubin, without jaundice, or of the total serum cholesterol content. This is mentioned merely to emphasize the belief that these two groups simply represent variations of the same disease, rather than distinct entities.

In a number of other instances in the series, in addition to the case referred to, the transition from hepatitis to cirrhosis was well substantiated by serial biopsy observations. This had also been the experience of Roholm and Krarup,¹⁶ Dible, McMichael and Sherlock,¹⁷ and Axenfeld and Brass.¹⁸

The present study reveals that in considering etiologic factors in cirrhosis it is necessary to pay strict attention to the type of clinical material studied, especially with regard to alcoholism. The patients making up the present series were referred, for the most part, from rural communities in the State of Minnesota, being sent to the University Hospital by their local physicians for diagnosis or treatment of relatively unusual conditions. The series of Ratnoff and Patek and

TABLE 4.—*History of Alcoholism and Antecedent Jaundice in 100 Cases of Hepatic Cirrhosis (1935 to 1945)*

	67 Males	33 Females
Alcoholism.....	23 (34.3%)	2 (6%)
Antecedent jaundice.....	20 (30%)	13 (40%)
Hepatitis.....	8 (12%)	9 (27%)

of Eppinger, which were alluded to at the outset, were drawn mainly from the routine admissions to large municipal hospitals, so that the incidence of alcoholism is high, as might be expected. It is interesting to contrast the incidence of antecedent jaundice and alcoholism in these two series with that found in the present study (table 3).

The difference noted in table 3 is not believed to be due to any protective effect of alcoholism against hepatitis but is regarded simply as an expression of the type of material studied. In other words, because our material included a smaller percentage of persons with alcoholism the factor of previous hepatitis comes into better perspective. This is brought out even more clearly if the male and female groups

16. Krarup, N. B., and Roholm, K.: The Development of Cirrhosis of the Liver After Acute Hepatitis, Elucidated by Aspiration Biopsy, *Acta med. Scandinav.* **108**:306-331, 1941.

17. Dible, J. H.; McMichael, J., and Sherlock, S. P. V.: Pathology of Acute Hepatitis: Aspiration Biopsy Studies of Epidemic, Arsenotherapy and Serum Jaundice, *Lancet* **2**:402-408 (Oct. 2) 1943.

18. Axenfeld, H., and Brass, K.: Klinische und biopsische Untersuchungen über den sogenannten Icterus catarrhalis, *Frankfurt. Ztschr. f. Path.* **57**:147-236, 1942.

are considered separately (table 4). Thus in the female group, with a relatively low incidence of alcoholism, the incidence of previous hepatitis is more than twice that in the male group, a greater proportion of whom were alcoholic.

SUMMARY

The present data reveal that in the material studied a history of a previous episode of infectious hepatitis was obtained in a significantly greater proportion of patients with cirrhosis than in a similar group without hepatic disease. This lends support to the concept that in certain cases the hepatitis runs a chronic or recurrent course, ultimately leading to the clinical and pathologic picture of cirrhosis of the liver. No attempt has been made to determine the proportion of cases of infectious hepatitis in which cirrhosis ultimately develops, but there is little doubt that this percentage is small. On the other hand, when cases of cirrhosis are considered, hepatitis is believed to be a precursor in a significant number. The study also emphasizes the importance of taking into account the type of material on which conclusions are based, as to etiologic factors in the production of cirrhosis. In the present series of cases of cirrhosis, which was widely drawn from rural communities, the incidence of alcoholism was relatively low, while that of antecedent hepatitis was relatively high, in contradistinction to previously reported series from large municipal hospitals, in which the reverse was true.

ANTITHYROID DRUGS: III

Comparison of Results of Newer Forms of Treatment of Thyrotoxicosis

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THE OBSCURITY of the fundamental disturbances in the body leading to the development of thyrotoxicosis has interfered with a direct approach in the therapy of this disease. Although much progress has been made in controlling it by surgical measures, a great deal is left to be desired, both as concerns the principles and the results of treatment. The ideal therapy is one which is simple, inexpensive, available to everyone, does not necessitate hospitalization, is not associated with significant toxic reactions and does not permit much invalidism. These ideals do not seem to be as reasonable an expectation with surgical treatment as with chemotherapy or physical therapy, but they must be developed to a greater extent.

PHYSIOLOGIC-CHEMICAL CONSIDERATIONS OF THYROID FUNCTION

Recent contributions¹ to the physiology of the thyroid have led to a clearer understanding of some of the problems of thyrotoxicosis.

This investigation was supported in part by a grant from the Committee on Research in Endocrinology, National Research Council.

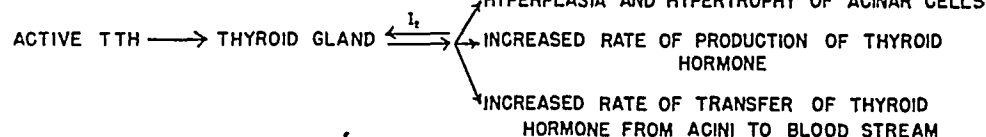
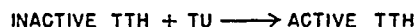
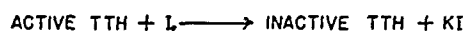
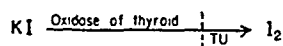
From the Thorndike Memorial Laboratory, Second and Fourth Medical Services (Harvard), Boston City Hospital, and the Department of Medicine, Harvard Medical School.

1. (a) Albert, A., and Rawson, R. W.: The Thyrotropic Hormone: Its Inactivation by Elemental Iodine and Its Reactivation by Thiouracil and other Goiter Producing Compounds, read before the American Society of Clinical Investigation, Atlantic City, N. J., May 27, 1946. (b) Rawson, R. W.; Moore, F. D.; Peacock, W.; Means, J. H.; Cope, O., and Riddell, C. B.: Effect of Iodine on the Thyroid Gland in Graves' Disease When Given in Conjunction with Thiouracil: A Two-Action Theory of Iodine, *J. Clin. Investigation* **24**:869 (Nov.) 1945. (c) De Robertis, E., and Nowinski, W. W.: The Proteolytic Activity of Normal and Pathological Human Thyroid Tissue, *J. Clin. Endocrinol.* **6**:235 (March) 1946. (d) Hertz, S.; Roberts, A., and Evans, R. D.: Radioactive Iodine as an Indicator in the Study of Thyroid Physiology, *Proc. Soc. Exper. Biol. & Med.* **38**:510 (May) 1938. (e) Hertz, S.; Roberts, A.; Means, J. H., and Evans, R. D.: Radioactive Iodine as an Indicator in Thyroid Physiology: II. Iodine Collection by Normal and Hyperplastic Thyroids in Rabbits, *Am. J. Physiol.* **128**:565 (Feb.) 1940. (f) Hertz, S., and Roberts, A.: Radio-

(Footnote continued on next page)

Whereas complete proof does not substantiate some of the hypotheses that have been advanced, they serve as logical working bases. The thyrotropic hormone tends to keep the thyroid gland active, the amount of stimulation varying in intensity with environmental changes. As is illustrated in chart 1, an excessive quantity of thyrotropin, as in toxic diffuse goiter, leads to (a) hyperplasia and hypertrophy of the acinar cells of the thyroid gland, (b) increased rate of production of thyroid hormone and (c) increased rate of transfer of thyroid hormone from the acini to the blood. The thyroid hormone exists in the acini as thyroglobulin. Except at the time of thyroidectomy or possibly with destructive lesions of the thyroid gland, thyroglobulin apparently does not exist in the blood stream, because it is too large a molecule

PRESUMPTIVE BIOCHEMICAL REACTIONS IN THE THYROID GLAND



TU = THIOURACIL

TTH = THYROTROPIC HORMONE

Chart 1.—Sites of therapy for toxic diffuse goiter. It is not known definitely that all these reactions take place in the body, but at present it seems likely that they do. It can be noted that iodine is an extremely active compound when it is in elemental form and that some of its reactions, as well as those of thiouracil, are antagonistic to each other, as far as the picture of thyrotoxicosis is concerned; moreover, the two compounds are antagonistic to each other.

to enter the blood vessel.² Proteolytic enzymes in the thyroid have been shown^{1c} to break down the globulin portion of thyroglobulin,

active Iodine as an Indicator in Thyroid Physiology: VI. Application of Radioactive Iodine in Therapy of 'Graves' Disease, *J. Clin. Investigation* **21**:624 (Sept.) 1942. (g) Means, J. H.: *The Thyroid and Its Diseases*, Philadelphia, J. B. Lippincott Company, 1937. (h) Salter, W. T.: *The Endocrine Functions of Iodine*, Cambridge, Mass., Harvard University Press, 1940. (i) Means, J. H.: Some New Approaches to the Physiology of the Thyroid, *Ann. Int. Med.* **19**:567 (Oct.) 1943.

2. Lerman, J.: Iodine Components of the Blood: Circulating Thyroglobulin in Normal Persons and in Persons with Thyroid Disease, *J. Clin. Investigation* **19**:555 (July) 1940.

permitting absorption of the active material into the blood stream; iodine inhibits this proteolytic action. Indeed, iodine participates in many reactions in the thyroid gland. It is added to tyrosine to form diiodotyrosine, and then two of these molecules react to form thyroxine.^{1b} However, before iodination can take place, the iodine which exists in the blood in the form of iodide must be changed to its free form, iodine, this reaction apparently being produced by an oxidase in the thyroid. Although iodine aids in the formation of the thyroid hormone, it can also cause a reversal of this effect by the inactivation of the thyrotropic hormone.^{1b} It is reasonably conceivable that the effect of iodide therapy in thyrotoxicosis is due to this inactivation, the variability in results depending on the competitive actions of iodine as well as the total amount of iodine available, the amount of thyrotropin produced, the rate of reactivation of thyrotropin, the amount of oxidase activity in the thyroid and many other factors.

Thiouracils and related compounds control thyrotoxicosis by decreasing the rate of manufacture of the thyroid hormone, attaining this result, conceivably, by the inhibition of the oxidase activity in the thyroid or by reacting with iodine. Apparently, by the inhibition of the oxidase reaction the conversion of iodide to iodine is blocked and, consequently, the synthesis of diiodotyrosine is antagonized. If the iodine of the thyroid must be liberated by an oxidase and if the assumption is correct that thiouracil inhibits the oxidase reaction, it would seem unnecessary to assume that the capacity of thiouracil to react with iodine plays a significant antithyroid role, because the iodine would remain in the form of iodide and, hence, would not react with thiouracil. Moreover, the amount of antithyroid action of the thiouracils is not proportional to the capacity of the compounds to react with iodine, forming thiouracil disulfide and an iodide. For example, 6-aminothiouracil and thiouracil react about equally with iodine, but the latter has a thousand times as much antithyroid action in rats.³

The fact that thiouracil activates thyrotropic hormone may explain the increase in the size of the goiter and the increase in manifestations of malignant exophthalmos that occur in a few patients while they are still thyrotoxic.

MODES OF THERAPY FOR THYROTOXICOSIS

There are a number of structures that modify the rate of metabolism in the body, especially the central nervous system, pituitary and thyroid as well as the body cells as a whole, as shown in chart 2. Moreover, these units exert a significant effect on one another, directly and indirectly. Consequently, it is not surprising to note that in the treat-

3. Miller, W. H.; Roblin, R. O., Jr., and Astwood, E. B.: Studies in Chemotherapy: XI. Oxidation of 2-Thiouracil and Related Compounds by Iodine, *J. Am. Chem. Soc.* **67**:2201 (Dec.) 1945.

ment of thyrotoxicosis attempts have been made to influence the function of these entities. Psychotherapy alone is successful in some cases. Roentgenotherapy applied to the pituitary has been claimed to be of some success.⁴ In a small proportion of patients desiccated thyroid will decrease the size of the goiter and lower the basal metabolic rate.⁵ The latter may be a result of the iodide in the drug. Iodide causes a favorable response in many patients with thyrotoxicosis, presumably by the inactivation of thyrotropin. The "antihormone" effect produced by pituitary preparations from various species is apparently due to inactivation of the thyrotropic hormone, but the results of this therapy leave much to be desired.⁶ The production of thyroxin is decreased

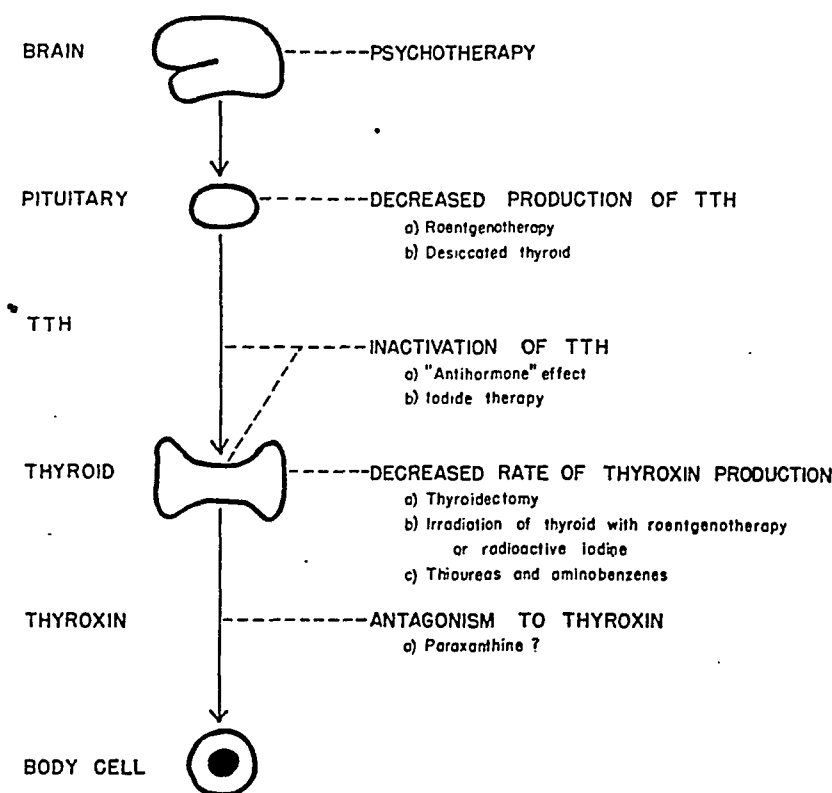


Chart 2.—The functions of each of these units have a direct or indirect effect on all the others; consequently, it is not surprising that therapy in thyrotoxicosis has been directed at many sites. The main site of action in some instances has not been clearly established.

by thyroidectomy, by irradiation of the thyroid gland and by the administration of thioureas or aminobenzenes. Little progress has been made

4. Thompson, W. O.: Personal communication to the author.

5. Rienhoff, W. F., Jr.: Changes Induced in Patients with Hyperthyroidism by Oral Administration of Desiccated Thyroid, *Bull Johns Hopkins Hosp.* **68**:538 (June) 1941.

6. Thompson, W. O.; Thompson, P. K., and Taylor, S. G.: III. Further Observations on Thyrotropic Activity of Anterior Pituitary, *West. J. Surg.* **48**: 633 (Oct.) 1940.

in obtaining drugs which inhibit the action of thyroxin, although a xanthine derivative has been thought to have this effect.⁷

DRUGS SELECTED FOR STUDY

In this clinic we have studied the effects of each of the foregoing methods of treatment of thyrotoxicosis, but in this report we are presenting results of therapy with only ortho-phenylenethiourea, thiothymine (5-methylthiouracil), 6-methylthiouracil, 6-isobutylthiouracil, 6-propylthiouracil, 6-cyclopropylthiouracil, 6-butylthiouracil, thiourea, para-aminobenzoic acid, 2-aminothiazole, thiobarbital, ethyldiiodobras-sidate⁸ and radioactive iodine. The formulas of most of these compounds are shown in chart 3. The results of the administration of extremely large doses of ascorbic acid and alpha tocopherol are also given. In the selection of the various compounds for clinical study, the following points, especially, were borne in mind. Thiouracil was recognized early as being exceedingly effective in the control of thyrotoxicosis, but the toxic reactions which it produced were of a greater severity than was desired. In the choice of a substitute it was not considered imperative to use compounds which had any greater antithyroid effect in rats than thiouracil, because (a) larger doses could be used if necessary and (b) the activities of the compounds in human beings are not always of the same relative order as they are in rats. These factors were the basis for testing clinically the effects of ortho-phenylenethiourea, thiothymine and 6-methylthiouracil, even though their antithyroid activity in rats was similar to that of thiouracil. There was an additional reason for the interest in thiothymine, or 5-methylthiouracil, based on the following observations⁹: A. Cytosine occurs more or less in equal concentration in the nucleus and cytoplasm of the cells of the body. B. Thymine exists chiefly in the nucleus. C. Uracil is found largely in the cytoplasm. Neither the beneficial nor the toxic effects of thio-uracil have been located as to site of action. By testing sulfur derivatives of cytosine and thymine, a compound which normally is

7. (a) Carter, G. S.; Mann, F. G.; Harley-Mason, J., and Jenkins, G. N.: Paraxanthine as a Natural Antithyroid Substance, *Nature*, London **151**:728 (June 26) 1943. (b) Carter, G. S., and Jenkins, G. N.: Distribution of Anti-thyroid Activity in Tissues, *ibid.* **154**:639 (Nov. 18) 1944.

8. Most of the compounds used in this study were supplied by Mr. W. A. Lott of the Squibb Institute, New Brunswick, New Jersey. The 6-propylthiouracil and para-aminobenzoic acid were obtained from Dr. S. M. Hardy, Lederle Laboratories, Inc., Pearl River, New York. The ethyldiiodobras-sidate was supplied by Dr. E. Oppenheimer, Ciba Pharmaceutical Products, Summit, New Jersey, and the thiobarbital was obtained from Dr. G. R. Hazel, Abbott Laboratories, Chicago, Illinois. Part of the 6-isobutylthiouracil was obtained from Dr. R. A. Harte, Arlington Chemical Company, Yonkers, New York. We are grateful to these persons and their companies for the extensive aid that we have been given.

9. Dempsey, E. W.: Personal communication to the author.

confined to the nucleus, it is conceivable that with one of the compounds good effects might be obtained without the bad effects. However, the inability to obtain thiocytosine made this investigation incomplete.

It was also desirable to test compounds with antithyroid action stronger than thiouracil, because if this stronger action were present in human beings, as well as in rats, a smaller dosage would be required

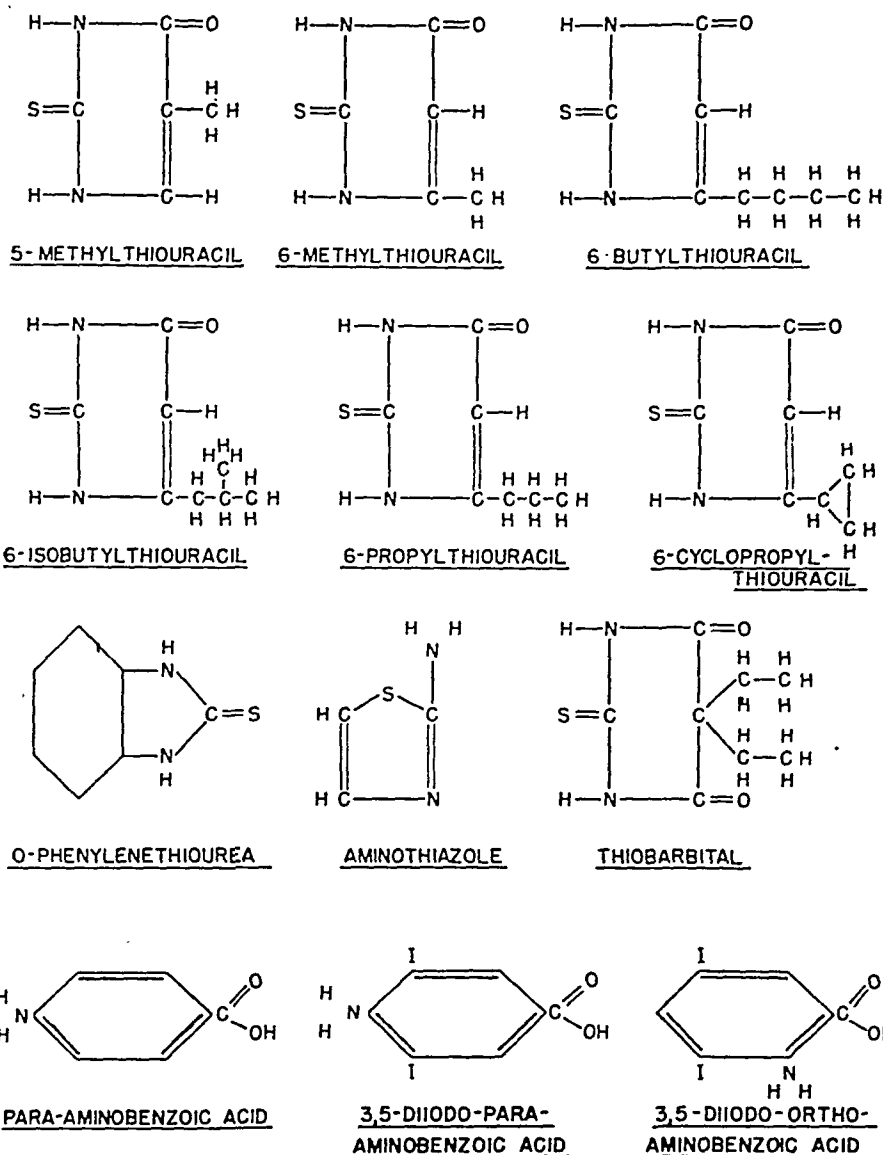


Chart 3.—Structural formulas of some of the compounds tested clinically. Note that all the drugs are derivatives of thiourea or are aminobenzenes.

and perhaps the toxic reactions would be less frequent. However, the rate of metabolism of the compounds, their distribution and physiologic-chemical properties are also to be considered. For example, if a compound is three times as active as thiouracil, it may be given in one-third the quantity of the latter. However, if it is maintained

in the body for three times as long and if other properties of the compound are like those of thiouracil, then it can be expected to be as toxic. These factors were borne in mind in testing 6-isobutylthiouracil, 6-cyclopropylthiouracil and 6-butylthiouracil.

It was a matter of considerable interest to test iodinated thioureas and iodinated aminobenzenes. It was hoped that the great affinity of the thyroid gland for iodine might lead to a concentration of the active antithyroid agent in the gland, thereby permitting the use of a much smaller dosage than would otherwise be necessary, and, consequently, with the smaller amount of drug in the body, toxic reactions would be of less significance. Consideration was given to two possibilities which might interfere with iodine's causing any potentiation of antithyroid effect: A. if the aminobenzenes or thioureas depend for their antithyroid activity on the inhibition of the action of a thyroid oxidase, the avidity of the thyroid for iodine might be abolished since the oxidase could not react with the iodine. B. If the activity of the thioureas and aminobenzenes depends on their capacity to react with the iodine of the body, this capacity might be interfered with, somewhat, by the introduction into the body of a compound which is already partially saturated with iodine. It was also borne in mind that in the disintegration of the iodinated compound iodide would probably be liberated and, consequently, an antithyroid effect might be produced, as happens in many patients with thyrotoxicosis treated with potassium iodide. On the other hand, the presence of the extra supply of iodide in the body might reduce the effectiveness of the thioureas. It was not possible to obtain iodinated thiouracils without having a substituent attached to the sulfur atom, and this substitution abolished the antithyroid activity.¹⁰ Two iodinated aminobenzenes were given a clinical trial, 3, 5-diiodo-para-aminobenzoic acid and 3, 5-diiodo-ortho-aminobenzoic acid.¹⁰

In the investigation of sodium diiodobrassidate, an iodinated fatty acid, it was desired to have a more or less constant liberation of iodine in the body and, possibly, thereby produce more effective results than are obtained by the use of the rapidly absorbed and rapidly excreted solution of potassium iodide. To insure saturation of the body with iodine, potassium iodide was given in conjunction with the sodium diiodobrassidate in 8 cases.

Vitamin E and ascorbic acid were given in large doses. Each compound was given to a separate person. These substances were given as representative of antioxidants and reducing compounds respectively, and it was desired to note their effect on thyrotropin, as well as on consumption of oxygen.

10. Williams, R. H., and Kay, G. A.: Further Studies on the Correlation of Chemical Structure and Antithyroid Effect, to be published.

The other compounds, consisting of thiourea,¹¹ para-aminobenzoic acid,¹² 2-aminothiazole,¹³ thiobarbital,¹⁴ 6-propylthiouracil¹⁵ and radioactive iodine,¹⁶ have been studied also by other investigators.

METHOD OF STUDY

The goitrogenic effect of each of the compounds was investigated,¹⁰ with the exception of thiobarbital and ethyldiiodobrossidate. The rate of absorption, distribution, destruction and excretion of some of the drugs was studied.¹⁷ The toxic effects were tested in rats by the administration of each compound in the drinking water; the concentration of the thioureas used was 0.1 per cent, and of the aminobenzenes, 1 per cent. After noting the effect of each on growth for an interval of about two or three weeks, the animals were killed. The viscera were examined, and sections for study, microscopically, were made of the liver, kidneys, spleen, pancreas, adrenals and gonads.¹⁰ All the compounds that had not been studied clinically were given to patients, without disease of the thyroid, who bore an extremely poor prognosis. These patients were given, for an interval of from two to three weeks, doses which although small at first were increased to three times or more the amount that was expected to be used in the patients with thyrotoxicosis. Toxic effects were looked for, especially in the skin, the liver, the kidneys and the blood.

Some of the thyrotoxic patients had no previous therapy, while others had received one or more antithyroid drugs. In some instances suboptimal doses of several compounds were used in order to compare their effectiveness. In a few instances the patient was permitted to have a relapse in his disease one or more times in order to have a standard comparison of the response to treatment with various drugs.

For example, 1 patient was treated for successive intervals of several weeks with thiouracil, isobutyl, propyl and cyclopropyl derivatives of thiouracil, para-aminobenzoic acid and aminothiazole respectively. Nineteen thyrotoxic persons were treated with the isobutyl, propyl and cyclopropyl derivatives; 25 were treated with only the latter two compounds. Several patients had more than one course of therapy with the same drug. In all, there were 112 thyrotoxic patients who were given two hundred and twenty-two courses of therapy, not including previous

11. Astwood, E. B.: Treatment of Hyperthyroidism with Thiourea and Thiouracil, *J. A. M. A.* **122**:78 (May 8) 1943.

12. Berman, L.: Human Thyrotoxicosis: Response to Para-Aminobenzoic Acid, *Proc. Soc. Exper. Biol. & Med.* **59**:70 (May) 1945.

13. Perrault, M., and Bovet, D.: Aminothiazole in the Treatment of Thyrotoxicosis, *Lancet* **1**:731 (May 18) 1946.

14. Astwood, E. B.: Some Observations on Use of Thiobarbital as an Anti-thyroid Agent in the Treatment of Graves' Disease, *J. Clin. Endocrinol.* **5**:345 (Oct.) 1945.

15. Astwood, E. B., and Vanderlaan, W. P.: Thiouracil Derivatives of Greater Activity in the Treatment of Hyperthyroidism, *J. Clin. Endocrinol.* **5**:424 (Dec.) 1945.

16. (a) Hertz, S., and Roberts, A.: Radioactive Iodine in Thyroid Physiology, *J. A. M. A.* **131**:81 (May 11) 1946. (b) Chapman, E. M., and Evans, R. D.: Radioactive Iodine in Hyperthyroidism, *ibid.* **131**:86 (May 11) 1946.

17. Williams, R. H., and Kay, G. A.: Comparisons of the Absorption, Distribution, Destruction and Excretion of Thiouracils and Thioureas, *Arch. Int. Med.*, to be published.

treatment with thiouracil,¹⁸ tetramethylthiourea,¹⁹ diethylthiourea¹⁹ or regular iodide therapy. The duration of each course of therapy is indicated in table 1.

The dosage of drug selected for thyrotoxic patients was based on the relative antithyroid effects of the compounds in rats, as compared to those of thiouracil. However, with each compound the doses used in the first few cases were too small. In the first few weeks of treatment the medication was given three or more times daily, at intervals widely spread throughout the day. Most of the patients were not hospitalized. In this instance they were examined at intervals of about two weeks for the first two months and with decreasing frequency thereafter. A determination of the basal metabolic rate and a white blood cell count were done at most of the visits. In some of the patients estimations were made of the amount of drug in the blood and urine.¹⁷

RESULTS

In view of the fact that several compounds differed in antithyroid potency only to a slight extent, the clinical and basal metabolic response

TABLE 1.—*Duration of Treatment*

Drug	Weeks							Total
	0 to 2	2 to 4	4 to 6	6 to 8	8 to 10	10 to 12	Over 12	
	Number of Patients							
Ortho-phenylenethiourea.....	3	6	3	1	3	1	..	17
Thiothymine.....	2	2	1	..	1	1	1	8
6-Methylthiouracil.....	3	1	1	2	1	..	3	11
6-Isobutylthiouracil.....	2	6	4	5	5	14	7	43
6-Propylthiouracil.....	..	4	3	5	9	2	16	39
6-Cyclopropylthiouracil.....	..	12	14	11	11	4	6	58
6-n-butylthiouracil.....	..	1	1	2	4
Para-aminobenzoic acid.....	..	5	2	1	8
3,5-Diiodo-para-aminobenzoic acid....	2	6	1	9
2-Aminothiazole.....	3	3	2	1	9
3,5-Diiodo-ortho-aminobenzoic acid...	..	3	3
Thiobarbital.....	1	..	1
Ethyldiiodobrassidate.....	6	3	2	..	1	12
								222

of most of the patients, as well as the dosage range, is indicated in table 2. In table 3 are presented the detailed changes in metabolic rate in selected cases. In table 4 is presented the course of certain patients who were treated, serially, with several compounds. In general, these patients did not respond as well as did the average subject to any of the drugs. Most of the values given for basal metabolic rates, especially the ones given in tables 3 and 4, were a good indication of the clinical condition of the patient. When there was a discrepancy between these observations, the metabolism test was usually repeated within a few days.

18. Williams, R. H.: Thiouracil Treatment of Thyrotoxicosis: I. The Results of Prolonged Treatment, *J. Clin. Endocrinol.* 6:1 (Jan.) 1946.

19. Williams, R. H.: Antithyroid Drugs: I. Tetramethylthiourea and Diethylthiourea, *J. Clin. Endocrinol.* 5:210 (May-June) 1945.

TABLE 2.—*Clinical and Basal Metabolic Response of Patients to Drugs Used*

Response			Daily Dosage, Gm.	Response			Daily Dosage, Gm.
Basal Meta-bolic Rate *	Clinical	Weeks		Basal Meta-bolic Rate *	Clinical	Weeks	
Ortho-phenylenethiourea							
	++	..	0.1 to 0.2	+18 to - 9	+++	8	0.05
+64 to +50	+	3	0.6 to 0.8	+23 to +26	0	8	0.075
+39 to + 5	+++	7	0.3 to 0.5	+33 to - 1	+++	2	0.125
+45 to + 7	+++	4	0.3	+29 to +17	+	10	0.075
+28 to + 7	+++	2	0.2		0	3	0.075
+50 to - 1	+++	4	0.4	+27 to +26	+	9	0.075 to 0.1
	++	2	0.5	+22 to +13	+	6	0.075
+65 to +17	++	2	0.4 to 0.8	+29 to +30	0	4	0.075
+85 to + 8	+++	1	0.3	+25 to +20	+	17	0.075 to 0.15
+73 to +52	+	1	0.8	+16 to + 9	+++	8	0.05 to 0.1
+79 to +31	+	8	0.4 to 1.0	+50 to +29	+	9	0.075 to 0.15
	+	1	0.6	+56 to +58	0	14	0.075 to 0.3
+20 to +10	+++	2	0.6	+40 to +23	+++	5	0.075 to 0.125
				+50 to +55	0	8	0.05 to 0.15
				+40 to +15	++	8	0.075 to 0.15
				+40 to +37	0	12	0.075 to 0.15
				+37 to +20	++	4	0.15
				+40 to + 1	+++	9	0.1 to 0.15
Thiothymine							
+36 to +17	+++	8	0.3 to 0.5	6-Cyclopropylthiouracil			
	+++	10	0.1 to 0.3		+++	4	0.1
+27 to + 7	+++	2	0.3	+36 to +16	++	4	0.1 to 0.15
+49 to +10	+++	9	0.3 to 0.4	+27 to + 9	+++	2	0.1
+36 to + 9	+++	6	0.3 to 0.4	+35 to +28	++	5	0.05
	+	1	0.2 to 0.4	+26 to - 1	+++	10	0.1 to 0.15
	++	3	0.4 to 0.5	+26 to +33	0	2	0.1
6-Methylthiouracil							
+49 to + 9	+++	1	0.3 to 0.6	+24 to - 7	+++	3	0.15
+37 to -10	+++	3	0.3	+20 to 0	+++	6	0.05 to 0.1
+64 to +12	+++	7	0.3	+26 to +11	+++	6	0.1 to 0.15
+22 to 0	+++	6	0.3	+70 to +30	++	4	0.1 to 0.15
+34 to 0	+++	4	0.2 to 0.3	+29 to +23	++	7	0.15
+35 to +26	++	8	0.3	+26 to +23	++	3	0.15
+59 to + 2	+++	8	0.1 to 0.3	+30 to - 3	+++	10	0.1 to 0.2
+64 to - 1	+++	4	0.4	+20 to +28	+	5	0.15
+26 to + 9	+++	7	0.3 to 0.5	+35 to + 7	+++	3	0.1
+51 to +31	+	1	0.3	+29 to +42	0	9	0.15 to 0.2
6-Isobutylthiouracil							
+28 to +25	0	11	0.03 to 0.09	+58 to +30	+	4	0.15 to 0.2
+15 to + 3	+++	2	0.09	+55 to +55	0	6	0.15
+26 to +11	+++	12	0.03 to 0.15	+16 to + 6	+++	2	0.1
+18 to + 4	+++	6	0.03 to 0.1	+15 to +21	+++	7	0.15 to 0.2
	0	2	0.06	+23 to +10	+++	3	0.1
+29 to + 6	+++	4	0.06 to 0.09	+100 to +34	++	2	0.15
+30 to + 6	++	2	0.06	+37 to +18	++	3	0.3
+39 to 0	+++	5	0.06 to 0.1	+20 to + 3	++	6	0.15
+37 to +27	0	10	0.03 to 0.12	+58 to - 1	+++	9	0.1 to 0.15
+28 to + 4	+++	2	0.09	+32 to -12	+++	2	0.1
+19 to +63	0	3	0.06	+46 to +13	+++	4	0.15
+64 to +54	+	4	0.06 to 0.1	+16 to +14	+++	4	0.01
+25 to + 8	+++	6	0.03 to 0.06	+34 to +10	+++	3	0.15
+30 to +11	0	3	0.03 to 0.09	+37 to + 3	+++	7	0.3
+39 to +13	++	9	0.06 to 0.15	+46 to +47	+	2	0.25
+31 to +29	++	12	0.09 to 0.15	+26 to +12	+++	2	0.2
+25 to +45	+	10	0.09 to 0.25	6-Butylthiouracil			
+38 to +17	++	8	0.06 to 0.1	+49 to + 2	+++	3	0.09
+26 to +13	+++	8	0.09 to 0.15	+43 to + 4	+++	6	0.09 to 0.15
+20 to +25	0	9	0.03 to 0.12	+13 to + 5	+++	3	0.09 to 0.15
+33 to +16	+++	11	0.06 to 0.12	+42 to +14	++	2	0.15
+55 to +50	0	10	0.09 to 0.15	Para-aminobenzoic Acid			
+53 to +40	+	8	0.09 to 0.3	+56 to +82	—	6	3.0 to 6.0
+76 to +40	+	13	0.09 to 0.2	+45 to +52	0	2	1.5
+38 to - 3	+++	6	0.09 to 0.15	+11 to 0	+	4	1.5
+26 to +12	+++	10	0.09 to 0.2	+57 to +14	+++	17	1.5
+60 to +12	++	8	0.09 to 0.15	+42 to +64	—	5	1.25 to 3.0
+44 to + 3	+++	12	0.1 to 0.15	+24 to +38	0	3	1.75
+31 to +40	+	12	0.09 to 0.25	+39 to +73	—	2	1.5
+47 to +24	++	4	0.09 to 0.15	- 8 to +25	—	2	5.0
+45 to +42	+	2	0.15	3,5-Diiodo-para-aminobenzoic Acid			
6-Propylthiouracil							
+25 to + 2	+++	4	0.075	+30 to +32	—	6	0.2 to 0.8
	+++	15	0.075 to 0.125	+42 to +12	++	2	0.6
				+35 to 0	+++	4	0.4 to 0.8
				+20 to +27	+	7	0.6 to 0.8
				+47 to +30	+++	2	0.6

TABLE 2.—*Clinical and Basal Metabolic Response of Patients to Drugs Used*
—Continued

Response				Response			
Basal Meta- bolic Rate *	Clinical	Weeks	Daily Dosage, Gm.	Basal Meta- bolic Rate *	Clinical	Weeks	Daily Dosage, Gm.
3,5-Diiodo-para-aminobenzoic Acid—Continued							
+50 to +52	+	2	1.0		0	4	0.45
+58 to +34	+	2	0.6 to 1.0	+21 to +20	0	3	0.8
+41 to +1	+++	2	0.6 to 1.6				
3,5-Diiodo-ortho-aminobenzoic Acid				Thiobarbital			
+62 to +44	+	3	1.0 to 2.0	+45 to +28	++	10	0.09 to 0.15
+12 to — 6	++	3	0.25				
+5S to +25	++	2	0.75				
2-Aminothiazole				Ethylidiodobrossidate			
	0	3	0.3 to 0.6	+47 to +21	++	4	0.9†
— 2 to +32	— — —	2	0.3	+34 to +20	+	4	0.9†
+33 to +1	+++	4	0.6	+22 to +29	0	4	1.8
+44 to +47	+	3	0.6	+26 to +14	+++	5	1.8
— 3 to +82	— — —	6	0.15	+57 to +18	++	4	0.9†
+30 to ?	0	2	0.6	+36 to +2	+++	5	0.9†
				+88 to +30	+	4	1.8
				+23 to +7	+++	3	0.9
				+60 to +15	+++	8	1.8 to 2.7†
				+97 to +12	++	6	1.8‡§
				+20 to — 1	+++	7	1.8‡§
				+35 to +45	0	4	1.8‡§

* The values for the basal metabolic rate presented are the lowest ones before treatment and either the lowest one following treatment or the first normal figure obtained. The approximate time required to obtain this response is indicated in weeks. The clinical response is graded with + marks, three plus signs indicating an essentially complete disappearance of the clinical manifestations of thyrotoxicosis. When no change in the clinical state of the patient occurred, this is designated with "0." The number of minus marks indicates the extent to which the thyrotoxicosis became worse. The results in patients who were recently treated for more than a few days with potassium iodide are omitted. In a few instances, indicated by a dash, the tests for basal metabolism were not performed at appropriate times.

† Potassium iodide also was given.

§ Intramuscular injections of sodium diiodobrossidate, 300 mg. daily, also were given.

Orthophenyleneithiourea.—Seventeen patients were treated with this compound. It was not consistently as effective as was thiouracil in comparable doses. However, in some patients no more than 0.2 or 0.3 Gm. daily were ever required. In a few instances the basal metabolism had become normal within two weeks. On the other hand, 1 patient did not show a complete response during an interval of eight weeks in which total daily dosages which were increased gradually from 0.4 to 0.8 Gm. were used. When iodide therapy supplemented the treatment with ortho-phenyleneithiourea a rapid response occurred.

In 5 of the 17 patients a febrile reaction to this drug developed. In 2 patients fever appeared at the end of one week, and in 1 it appeared after two weeks. In a fourth patient fever, arthritis and leukopenia developed after treatment for ten days. In a fifth patient fever developed after therapy for a period of five weeks and was associated with arthritis and a white blood cell count of 3,100. This patient had previously reacted to thiouracil with fever and to tetramethylthiourea with a maculopapular rash.

Thiothymine.—Thiothymine, or 5-methylthiouracil, was used in the treatment of 8 patients, the longest period of treatment being four months. Its antithyroid effect was less than that of thiouracil or

TABLE 3.—*Response to Treatment as Illustrated in Certain Cases**

Date	Basal Metabolic Rate	Daily Dosage, Gm.	Date	Basal Metabolic Rate	Daily Dosage, Gm.	Date	Basal Metabolic Rate	Daily Dosage, Gm.
Ortho-phenylenethiourea			5/ 9	+69	0.4	6/26	+29	1.5
5/ 2	+39	0.3	5/12	+36	0.4	7/ 3	+53	1.5
5/ 8	+36	0.3	5/19	+44	0.4	7/12	+73	1.5
5/11	+20	0.3	5/28	+24	0.4			
5/17	+16	0.3	6/ 8	— 1	0.4	6/26	+57	1.5
5/24	+61	0.3				7/ 5	+62	1.5
5/29	+47	0.5	5/11	+26	0.4	10/20	+14	1.5
6/ 2	+19	0.5	5/14	+22	0.4			
6/ 8	+13	0.5	5/21	+17	0.3	3,5-Diiodo-para-aminobenzoic Acid		
6/16	+11	0.3	6/ 5	+42	0.3			
6/23	+ 5	0.2	6/20	+38	0.5	6/27	+35	0.4
			6/29	+ 9		7/ 9	+40	0.8
5/28	+31	0.3	6-Isobutylthiouracil			7/23	0	0.0
6/ 4	+19	0.3	11/25	+29	0.06			
6/11	+20	0.3	12/ 5	+41	0.06	7/ 9	+50	1.0
6/19	+ 7	0.2	12/14	+21	0.09	7/14	+35	1.0
			12/21	+ 6	0.06	7/18	+16	1.0
5/15	+28	0.2	12/19	+28	0.09	7/23	+52	
5/23	+13	0.2	1/ 2	+ 4	0.09	7/ 3	+58	0.6
5/31	+ 7	0.2	1/ 8	—10	0.09	7/ 5	+56	1.0
			1/15	+ 5	0.09	7/12	+20	1.0
5/26	+50	0.4	12/10	+38	0.09	7/15	+31	1.0
6/ 5	+28	0.4	12/17	+31	0.09	7/20	+34	
6/19	+ 9	0.4	12/26	+27	0.09	7/ 2	+41	0.6
5/17	+79	0.4	1/ 4	+83	0.15	7/ 5	—	1.0
5/24	+53	0.4	1/14	+18	0.15	7/10	+ 6	1.0
6/ 2	+38	0.4	1/24	— 3		7/15	+15	1.0
6/11	+53	0.6	6-Propylthiouracil			7/17	—	1.6
6/20	+37	0.6	4/ 2	+40	0.1	7/20	+ 1	
6/27	+36	0.8	4/27	+31	0.15	3,5-Diiodo-ortho-aminobenzoic Acid		
7/ 5	+49	1.0	6/ 8	+ 1	0.05			
7/13	+31		4/15	+33	0.125	11/ 5	+62	1.0
Thiothymine			4/29	— 1	0.075	11/13	—	1.5
5/ 2	+49	0.3	5/20	+16	0.075	11/17	—	2.0
5/ 8	+42	0.3	6/10	+ 1	0.05	11/21	+31	2.0
5/16	+24	0.3	6-Cyclopropylthiouracil			11/28	+44	
5/25	+28	0.3	3/30	+27	0.05	2-Aminothiazole		
6/ 1	+26	0.4	4/16	+ 9	0.05	6/16	—11	0.3
6/ 8	+23	0.4	4/30	+16	0.05	6/27	+33	0.6
6/15	+13	0.4	5/15	— 4	0.05	7/ 9	+12	0.6
7/ 5	+10		6/ 4	— 4	0.05	7/24	+ 1	0.6
5/14	+36	0.3	5/ 8	+26	0.1	Ethyl-diiodobrassicinate		
5/21	+30	0.3	6/ 7	+20	0.15			
5/28	+21	0.3	6/26	+19	0.15	10/26	+47	0.9
6/11	+21	0.4	7/19	— 1	0.05	11/ 5	+43	1.8
6/25	+ 9	0.3	4/16	+23	0.1	11/23	+21	1.8
7/11	+ 6	0.3	5/ 6	+10	0.05			
8/ 4	+14	0.3	6/ 5	+11	0.1	9/15	+36	0.9
9/ 8	+ 9		7/ 8	— 2		9/29	+14	0.9
3/28	+21	0.3	6/ 3	+37	0.3	10/20	+ 2	0.9
4/ 6	+ 7	0.3	6/26	+28	0.3	11/17	+29	
4/12	+ 3		7/ 6	+18	0.3			
			7/23	+ 3		1/21	+88	1.8
6-Methylthiouracil			6-Butylthiouracil			2/18	+30	1.8
5/15	+64	0.3	1/21	+49	0.69	6/10	+70	1.8
6/ 2	+48	0.3	1/31	+16	0.09	9/29	+60	1.8
6/22	+22	0.3	2/13	+ 2	0.09	10/15	+38	1.8
7/ 7	+12		Para-aminobenzoic Acid			10/30	+24	1.8
4/21	+59	0.3	6/19	+42	1.5	11/12	—	2.7
5/ 5	+27	0.3	7/11	+22	3.0	11/19	+15	2.7
5/26	+10	0.3	7/18	+88	3.0	11/27	+22	0.0
6/23	+ 2	0.1	7/24	+64		9/19	+97	1.8
8/15	+11	0.05				9/28	+37	1.8
						10/ 2	+49	1.8
						10/ 9	+22	1.8

* Each group of figures represents the data on a separate patient. In a few instances, indicated by a dash, the tests for basal metabolism were not performed at appropriate times.

ortho-phenylenethiourea. In 1 patient the basal metabolic rate was not quite normal after receiving about 0.4 Gm. daily for eight weeks. In another patient nine weeks were required to obtain a complete response. On the other hand, in another patient there was a remission of the disease in two weeks, with the use of only 0.3 Gm. daily. A moderate febrile response developed in 1 patient after taking thiothymine for eight days.

6-Methylthiouracil.—Eleven patients were treated with 6-methylthiouracil. The antithyroid effect seemed to be somewhat stronger with this compound than with thiouracil. A dosage greater than 0.4 Gm. daily was apparently unnecessary. A complete clinical response was obtained within one to eight weeks in all patients. In 1 patient the basal metabolic rate decreased from plus 49 to plus 9 within eight days. In another patient it decreased from plus 37 to minus 10 within three weeks. The longest interval during which it was used was six months.

In 1 patient there developed a slight maculopapular eruption after receiving treatment for two months, but it disappeared within a few days in spite of continued therapy. In another patient a temperature of 103 F. developed and the fever persisted for two days after cessation of therapy.

6-Isobutylthiouracil.—6-Isobutylthiouracil was used in the treatment of 43 patients with thyrotoxicosis. In the beginning, most of the patients were given doses of the drug which were much too small; however, the quantity necessary varied a great deal. In a few cases no more than 60 mg. daily were ever required. On the other hand, in some instances it was necessary to administer from 0.2 to 0.3 Gm. daily for several weeks before a complete response was obtained. The maintenance dosage was determined in only a few cases and was approximately 0.1 Gm. daily. Itching of the skin was complained of by 4 persons, but no rash was seen. No other type of toxic reaction was observed.

6-Propylthiouracil.—Thirty-nine thyrotoxic subjects were treated with 6-propylthiouracil. This compound was found to be less potent than was indicated by Astwood's report.¹⁵ In a few instances administration of 75 mg. daily was sufficient to produce a disappearance of the thyrotoxicosis, but in others, as seen in tables 2 and 4, administration of 150 mg. or more daily for several weeks was ineffective. The maintenance dosage was found to be from 50 to 100 mg. daily. In none of the patients did toxic reactions to this drug develop, in spite of the fact that 1 patient had reacted to thiouracil with a rash and to tetramethylthiourea with fever. Another patient had reacted with leukopenia and rash to thiouracil and with fever and rash to tetramethylthiourea. In 1 patient fever had developed with the use

TABLE 4.—Comparison of the Potency of 6-Isobutyl, 6-Propyl and 6-Cyclopropyl Derivatives of Thiouracil

Drug	Date	Basal Metabolic Rate	Daily Dosage, Gm.*	Drug	Date	Basal Metabolic Rate	Daily Dosage, Gm.*	
Case 32				Case 256				
6-Isobutyl- thiouracil	12/ 3	+20	0.03	6-Isobutyl- thiouracil	11/ 9	+12	0.09	
	12/21		0.06		11/17	+20	0.09	
	1/ 3	+28	0.06		11/21	+35	0.09	
	1/17	+32	0.12		12/11	+53	0.09	
	2/ 5	+25	0		1/ 2	+69	0.15	
6-Propyl thiouracil	2/26	+40	0.075		1/10	+58	0.15	
	3/19	+34	0.075		1/17	+56	0.2	
	4/ 9	+38	0.125		1/25	+63	0.3	
	4/26	+35	0.15	Thiouracil	2/ 2	+40	0.4	
	5/13	+24	0.15					
6-Cyclopropyl- thiouracil	6/14	+20	0.15		6-Isobutyl- thiouracil	2/ 9	+18	0.3
	7/ 2	+28	0.15			2/16	+56	0.075
	7/19	+28	0.15			3/ 6	+47	0.075
					3/27	+63	0.075	
Case 51					4/10	+55	0.15	
6-Isobutyl- thiouracil	12/ 7	+33	0.06		4/24	+40	0.225	
	12/27	+25	0.09		5/ 9	+53	0.3	
	1/10	+26	0.09	6-Cyclopropyl- thiouracil	5/23	+58	0.2	
	1/24	+18	0.09			6/ 6	+36	0.25
	2/ 7	+16	0.12			6/19	+30	
6-Propyl- thiouracil	2/21	+16	0.05		Case 257			
	3/20	+23	0.1		6-Isobutyl- thiouracil	12/ 4	+76	0.09
	4/18	+ 9	0.025			12/13	+43	0.12
6-Cyclopropyl- thiouracil	5/10	+35	0.1			12/21	+36	0.09
	5/28	+ 7	0.05			12/29	+60	0.15
	7/16	+ 4	0.05			1/15	+51	0.15
Case 212					1/26	+70	0.15	
6-Isobutyl- thiouracil	11/24	+37	0.03		2/ 7		0.2	
	12/23	+35	0.09	6-Propyl- thiouracil	2/16	+39	0.2	
	1/ 9	+36	0.09			3/ 2	+40	0.075
	1/23	+28	0.12			3/19		0.125
6-Propyl- thiouracil	2/ 7	+27	0.075			4/ 5	+23	0.075
	3/23	+10	0.075	6-Isobutyl- thiouracil	Case 262			
	6-Cyclopropyl- thiouracil	4/11	+26		0.1		12/22	+26
4/25		+38	0.15			1/11	+20	0.09
5/10		+12	0.15			1/25		0.15
5/24		+11	0.15			2/ 4	+22	0.15
Case 249					2/19	+13	0.2	
6-Isobutyl- thiouracil	12/14	+31	0.09	6-Propyl- thiouracil	3/ 5	+12	0.075	
	12/27	+34	0.09			3/30	+15	0.1
	1/10	+58	0.15			4/13	+12	0.125
	1/22	+24	0.15			4/29	— 1	0.075
	2/ 5	+19	0.15			5/13	—13	0.025
	2/18	+28	0.15	6-Cyclopropyl- thiouracil	6/ 7	+ 9	0.05	
6-Propylthiouracil	3/ 4	+29	0.075			7/12	+26	0.2
	6-Cyclopropyl- thiouracil	4/ 1	+30		0.1	Case 264		
		4/15	+67		0.1	6-Isobutyl- thiouracil	12/11	+60
4/29		+47	0.15		1/ 2		+36	0.09
5/13		+19	0.15		1/16		+33	0.15
6/ 3		+39	0.2		1/23		+20	0.15
6/18	— 3			2/ 6	+12		0.15	
Case 251					3/ 2		0.09	
6-Isobutyl- thiouracil	12/14	+55	0.09		3/19	+27	0.15	
	12/28	+93	0.12	6-Cyclopropyl- thiouracil	4/ 5	+16	0.1	
	1/26	+60	0.15			4/18	+ 6	0.1
	6-Propyl- thiouracil	2/21	+50		0.075		5/ 3	— 8
3/23		+45	0.125			5/31	— 5	0.05
4/12		+42	0.15		Case 265			
6-Cyclopropyl- thiouracil	4/26	+29	0.15	6-Isobutyl- thiouracil	1/ 5	+44	0.1	
	5/21	+42	0.15			1/26	+19	0.15
	6/11	+42	0.2			3/ 2		0.1
6/27	+42	0.2	6-Cyclopropyl- thiouracil	3/16	+23	0.15		
					4/ 6	+47	0.1	
					4/20	+ 3	0.05	

TABLE 4.—Comparison of the Potency of 6-Isobutyl, 6-Propyl and 6-Cyclopropyl Derivatives of Thiouracil—Continued

Drug	Date	Basal Metabolic Rate	Daily Dosage, Gm.*	Drug	Date	Basal Metabolic Rate	Daily Dosage, Gm.*
	5/11	+4	0.05	6-Cyclopropyl-thiouracil	5/16	+37	0.3
	6/1	0	0.05		5/21	+50	0.3
	6/29	-11	0		5/24	+34	0.3
					5/29	+24	0.3
					6/3	+18	0.3
	Case 266				Case 276		
6-Isobutyl-thiouracil	12/22	+31	0.09	6-Propyl-thiouracil	4/1	+37	0.15
	1/19	+48	0.15		4/9	+26	0.15
	2/16		0.25		4/13	+24	0.15
	3/2	+20	0.15				
6-Propyl-thiouracil	3/16	+40	0.075	6-Cyclopropyl-thiouracil	4/25	+20	0.15
	4/6	+39	0.15		5/10	+17	0.15
	4/26	+20	0.15		5/23	+30	0.15
					6/6	+3	0.05
6-Cyclopropyl-thiouracil	5/10	+15	0.15	3,5-Diiodo-para-aminobenzoic acid	6/27	+35	0.4
	5/25	+34	0.15		7/9	+40	0.8
	6/15	+23	0.2		7/23	0	
6-Propyl-thiouracil	6/29	+21	0.2		Case 278		
	7/11	+21	0.2	6-Cyclopropyl-thiouracil	4/6	+53	0.1
	Case 273				4/25	+29	0.15
6-Propyl-thiouracil	2/19	+40	0.075		5/9	+25	0.15
	3/6		0.125		5/25	+22	0.15
	3/19	+32	0.125	2-Aminothiazole	6/12	-11	0.3
	4/13		0.15		6/27	+33	0.6
	4/20	+40	0.15		7/9	+12	0.6
	4/25	+34	0.15		7/24	+1	

* The dosages were prescribed on the date that is given on the same line. As soon as the use of one drug was discontinued, another was given. In a few instances, indicated by a dash, the tests for basal metabolism were not performed at appropriate times.

of ortho-phenylenethiourea. Two subjects had had a rash from the use of thiouracil and another patient had reacted to aminothiazole with a rash, fever and arthritis.

6-Cyclopropylthiouracil.—Fifty-eight thyrotoxic patients were treated with 6-cyclopropylthiouracil. In several cases never more than from 50 to 100 mg. of the drug was necessary to produce a remission in the thyrotoxicosis, as seen in tables 2 and 3. Yet in other cases, shown in tables 2, 3 and 4, administration of 150 mg. or more daily for several weeks was ineffective. The maintenance dose was from 50 to 100 mg. daily. No toxic effects were observed in any case, in spite of the fact that 1 patient had previously reacted to thiouracil with a rash, 1 had had a fever, rash and arthritis with the use of aminothiazole, 1 had reacted with fever and leukopenia to thiouracil and with fever and rash to tetramethylthiourea and 1 had reacted with a rash to thiouracil and with fever to tetramethylthiourea.

6-Butylthiouracil.—Only 4 thyrotoxic patients were treated with 6-butylthiouracil. Each of these persons experienced a satisfactory response in their disease, receiving from 90 to 150 mg. of the drug

daily. No toxic reactions occurred, except that in 1 patient there was a decrease in the white blood cell count to 3,000 after treatment for four weeks.

Para-Aminobenzoic Acid.—Eight thyrotoxic patients were treated with para-aminobenzoic acid. One patient experienced a rise in his basal metabolic rate from plus 56 to plus 82 within six weeks in spite of the fact that he received 1.5 Gm. daily for one week and 3.0 Gm. daily for five weeks. In 1 case, a normal metabolic rate having been obtained with the use of thiouracil, 0.5 Gm. of para-aminobenzoic acid was given daily as a maintenance dose. Within two weeks the basal metabolism had risen to plus 25 and the patient showed evidence, clinically, of a reappearance of the disease. However, when in addition to this therapy 0.1 Gm. of thiouracil was given daily, a clinical and metabolic response to normal resulted within about two weeks. To another patient 4.0 Gm. of para-aminobenzoic acid was given daily for two weeks in conjunction with 75 mg. of 6-propylthiouracil daily. This patient had received the latter dosage for the preceding six weeks, without any response. The supplemented therapy did not have any effect on the course of the disease. Another patient was given 1.5 Gm. daily for fourteen weeks. Her basal metabolic rate decreased from plus 57 to plus 14. No toxic effects from the drug were encountered.

3, 5-Diiodo-Para-Aminobenzoic Acid.—Nine patients were treated with 3, 5-diiodo-para-aminobenzoic acid, the dosage averaging about 0.8 Gm. daily. There is essentially the same amount of iodine in 0.6 Gm. of this compound as there is in 15 drops of a saturated solution of potassium iodide. The response varied a great deal in different patients. In 1 person the disease became slightly worse. In 3 patients there was only slight improvement, in 1 there was moderate improvement and in 3 there was a complete remission of the disease. Within nine days 1 patient showed a desirable response in his clinical status and basal metabolism, as shown in table 3, but in spite of continuation of the same dosage, 1.0 Gm. daily, within another five days he was definitely worse, as indicated clinically and by the metabolic rate. This phenomenon was observed in 2 other patients, and it might have occurred in another if treatment had been continued longer. No toxic effect was observed in any patient.

3, 5-Diiodo-Ortho-Aminobenzoic Acid.—Three patients with toxic diffuse goiter were treated with 3, 5-diiodo-ortho-aminobenzoic acid, doses ranging from 0.25 to 2.0 Gm. daily being used. Only slightly beneficial results were obtained, but no toxic effects were observed.

Aminothiazole.—Nine thyrotoxic patients were treated with aminothiazole daily, doses varying from 0.15 to 0.6 Gm. being used. In 1 patient 0.3 Gm. daily was not adequate for a maintenance dose, as

seen in table 3, but administration of 0.6 Gm. was sufficient to produce a remission in the disease. In 2 other patients daily doses of 0.15 and 0.3 Gm. respectively were inadequate in maintaining a normal basal metabolism that had been produced with thiouracil. Three patients showed no response to treatment within intervals of about two or three weeks although they received from 0.6 to 0.8 Gm. daily. After treatment for nine days an extensive dermatitis, resembling the type seen with the use of sulfathiazole, fever and severe arthritis involving many joints of the extremities developed in 1 patient. In another patient there developed hepatitis with severe jaundice, but it probably was infectious hepatitis. Neither of these patients had any untoward reactions to propylthiouracil or cyclopropylthiouracil before or after the aminothiazole therapy.

Thiobarbital.—One patient who had had a febrile response to ortho-phenylenethiourea was given iodide therapy for two months. Two weeks before the cessation of iodide treatment thiobarbital therapy was started and was continued for ten weeks in doses varying from 100 to 150 mg. daily. There was a slight reduction in the basal metabolism and a moderate improvement in the clinical condition of the patient. However, his white blood cell count decreased to 3,200, with 45 per cent polymorphonuclear neutrophilic leukocytes. The thiobarbital was replaced with 6-isobutylthiouracil, in doses of 0.06 Gm. daily, but since the white blood cell count was unchanged one week later, iodide therapy was instituted in the place of treatment with isobutylthiouracil. Because the white blood cell count remained around 3,200 even three weeks after cessation of therapy with the thiourea derivatives, thiobarbital was then given in doses of 90 mg. daily. Five days later the patient noticed anorexia, abdominal discomfort and dark urine. Three days thereafter he was intensely jaundiced and had definite impairment of hepatic function. It is uncertain whether his hepatitis was infectious or due to the administration of thiobarbital. After the patient recovered from the hepatitis and the leukopenia, he was given propylthiouracil in doses of from 125 to 150 mg. for four weeks, and thereafter he received cyclopropylthiouracil in doses of from 150 to 250 mg. for thirteen weeks, without untoward effect.

Other Thioureas.—Tetramethylthiourea and diethylthiourea were investigated clinically, and the results of these studies have been reported.¹⁹ Thiourea was given to 3 patients for intervals of from one to two weeks, but the patients complained of its taste and smell so much that it was discontinued.

Ethyldiiodobrassidate.—Twelve patients with thyrotoxicosis were treated with ethyldiiodobrassidate in doses varying from 0.9 to 2.7 Gm. per day. Essentially the same amount of iodine is present in 0.9 Gm.

of ethyldiiodobrassidate as is in 15 drops of a saturated solution of potassium iodide. In addition to this medication, which was in the form of tablets, 3 patients received, intramuscularly, ethyldiiodobrassidate in olive oil; 0.3 Gm. was given daily for about two weeks. Eight of the 12 subjects were also given standard treatment with potassium iodide. The response obtained was about the same as though potassium iodide alone had been used, some of the patients showing no response, some responding partially and others experiencing a complete disappearance of the thyrotoxic manifestations. Moreover, certain patients who responded well had a relapse of the disease in spite of continuous therapy. The persons receiving the iodinated lipid and no potassium iodide responded in about the same manner as the ones receiving both drugs. The additional diiodobrassidate given intramuscularly did not improve the results.

No untoward effects resulted from this form of therapy. A few of the patients preferred the diiodobrassidate to potassium iodide.

Ascorbic Acid.—A thyrotoxic patient who was given tests for basal metabolism daily for thirteen days was found to have a rate of from plus 35 to plus 46 per cent on all but two occasions. She was then given orally 100 mg. of ascorbic acid at hourly intervals from 5 a. m. until 9 p. m. and subcutaneously 0.5 Gm. every six hours. She was given this therapy on January 31, February 1 and until noon of February 2. At this time the previous regimen was discontinued. The patient was then given 1.0 Gm. of ascorbic acid, followed by 0.5 Gm. orally every five hours until after the determination of basal metabolism on February 3. One hour before this test 0.5 Gm. was given subcutaneously. The results of tests for basal metabolism were as follows: plus 39 per cent on January 30; plus 40 per cent on January 31; plus 39 per cent on February 1; plus 49 per cent on February 3, and plus 48 per cent on February 6. Thus the use of ascorbic acid did not influence the basal metabolism, nor did it have a definite effect on the clinical state of the patient. The thyroid gland enlarged slightly while the patient was receiving the ascorbic acid, but it is not definite that the enlargement was due to the therapy.

Alpha Tocopherol.—A patient with moderately severe thyrotoxicosis and thyrotoxic myopathy was found to have a basal metabolism of plus 58 per cent on January 5 and plus 51 per cent on January 8. On the latter date he was given 0.75 Gm. of alpha tocopherol phosphate in 2,000 cc. of isotonic solution of sodium chloride. This solution was given intravenously over an interval of seven hours. On this date he was also given 0.24 Gm. of alpha tocopherol intramuscularly and 0.6 Gm. orally in three divided doses. The following day, January 9, he received 0.2 Gm. orally at 5 a. m., 7 a. m. and 9 a. m. He was given

intramuscularly 0.24 Gm. at 5 a. m., 2 p. m. and 9 p. m. On January 10, he received orally 100 mg. every hour from 10 a. m. until 9 p. m. and intramuscularly, 0.24 Gm. at 5 a. m. and 2 p. m.

On January 10 he was also given 0.65 Gm. of alpha tocopherol phosphate, intravenously, between 9 a. m. and 11 a. m. The basal metabolism, determined fifteen minutes later, was plus 78 per cent. The following day it was plus 84 per cent; on January 9 it was plus 50 per cent. During the alpha tocopherol therapy the thyroid gland became definitely larger, the thyrotoxicity increased and the patient became much weaker.

Radioactive Iodine.—Five patients have been treated with radioactive iodine. Two of these were given 25 millicuries of iodine, with a half period of twelve hours. One subject had had no previous therapy, while the other had been treated with thiouracil for one year but received no treatment for one week preceding the radioactive iodide therapy. A complete remission was obtained in both patients within four months. The other 3 patients were given 25, 20 and 15 millicuries respectively, but insufficient time has elapsed thus far for proper evaluation of the results. No ill effects from the treatment have been observed so far. This type of therapy was particularly welcomed in 1 of these patients because he was 72 years of age and was bothered with severe thyrotoxic myopathy and acute rheumatoid arthritis. Moreover, he had a febrile response to ortho-phenylenethiourea and failed to respond to iodide therapy. While he was taking thiobarbital leukopenia and severe hepatitis developed. In spite of therapy for several months, he was in an unsatisfactory condition for thyroidectomy. Three other patients who needed this type of treatment were referred to Dr. Earl Chapman. One was a patient who had reacted to thiouracil with fever and in whom severe dermatitis associated with iodide therapy had developed. Another patient was an elderly woman who reacted to tetramethylthiourea with fever and to iodide with a severe rash. The third person was refractory with regard to iodide and had had malignant neutropenia with thiouracil treatment. Consequently, in each of these patients the usual forms of therapy were unsatisfactory and the risk associated with thyroidectomy was too great. Each has responded well to treatment with radioactive iodine.

COMMENT

In view of the fact that three relatively good types of treatment are available for thyrotoxic patients, the question often arises as to which is the best treatment—surgical intervention or administration of thioureas or radioactive iodine. A careful evaluation of the favorable and unfavorable results of each form of treatment will indicate that the treatment of choice varies with the individual case. However, there is left a fairly large proportion of patients in whom any one of the three types of therapy

is optional and may be determined partially by the temperament of the patient and by the physician. The problem is sometimes a difficult one to decide, especially when the physician considers the matter from an unprejudiced and scientific point of view. The problem will doubtless become easier as more is learned about the use of the thioureas and radioactive iodine. In the succeeding paragraphs are listed some factors which help govern the extent of usefulness of the three procedures.

A. Surgery.—The performance of a subtotal thyroidectomy for the treatment of thyrotoxicosis has one advantage over the use of thioureas or radioactive iodine in that there is more definite information about the long range results of therapy. With the use of the latter two forms of therapy undesirable results may appear which are unforeseen at present. On the other hand, with improvement in these methods of therapy more good results and fewer of the present poor results may be obtained. To be sure, the results with surgical treatment will also improve but probably not to as great an extent.

Surgical intervention would seem to be the treatment of choice when there is an extremely large nodular goiter. However, such glands have been observed to decrease slightly in size after the use of thiouracil and to a great extent after treatment with radioactive iodine. In some instances the most rapid remission from the disease is offered by surgical treatment. However, when consideration is given to the time required for the patient to recover completely from the operation, the interval is not infrequently as great as is required for the production of a complete remission with the use of radioactive iodine.

It has been proposed²⁰ that an operation is especially desirable when a toxic nodular goiter is present, because of its prophylactic value in the avoidance of the development of malignant changes of the thyroid gland. In the evaluation of this point, several other factors must be considered, as for example, the great rarity of malignant changes of the thyroid in patients with thyrotoxicosis. Means¹⁸ stated in his textbook, which covers the experiences of a large and active clinic for the treatment of thyrotoxic patients for a period of more than twenty years, "We have not seen cancer in persons who in the past have had toxic goiter." Whereas Dr. Means has recently informed me that he subsequently has seen a few instances of carcinoma of the thyroid in thyrotoxicosis and whereas a few cases have been reported by other authors, it can be concluded that "malignant" neoplasms of the thyroid gland in thyrotoxic patients are extremely rare.²¹

In a consideration of the results of surgical intervention, it must be borne in mind that surgical treatment is available to only a small minority

20. Beierwaltes, W. H., and Sturgis, C. C.: Remissions in Thyrotoxicosis After Thiouracil, *J. A. M. A.* **131**:735 (June 29) 1946.

21. Rogers, W. F., Jr.; Asper, S. P., Jr., and Williams, R. H.: To be published.

of the people. Consequently, in the assessment of the value of an operation the figures of a few specialized clinics should not be considered as applying to the problem as a whole. Moreover, even in the best clinics—for example, the Massachusetts General Hospital—better results are desirable. For instance,¹⁵ 2.6 per cent of the patients died during or soon after operation, myxedema developed in 2.3 per cent and hypoparathyroidism developed in 1.3 per cent. Thus far, none of these complications except myxedema has resulted from treatment with radioactive iodine, nor has recurrent paralysis of the laryngeal nerve, and none of them has resulted from the newer thiourea derivatives.

Treatment by means of surgical intervention presents a number of major problems that need not occur with either of the other forms of therapy. The patient must make emotional, financial and social adjustments for his hospitalization. He is subjected to a great deal of discomfort that is not associated with either of the other forms of treatment. The loss of time from work, nursing care, hospital bill and surgeon's fee add up to an amount which usually is greater than in the other forms of therapy.

Surgical Treatment or Radioactive Iodine.—One of these forms of therapy is indicated when an extremely large goiter is present. However, this is not necessarily so, particularly if the goiter is not nodular, because roentgenotherapy used in conjunction with thiouracils has given satisfactory results.¹⁸ An operation or radioactive iodine is indicated when serious toxic reactions to thioureas have occurred, although another thiourea derivative sometimes may be used satisfactorily. Rarely a patient will appear to be somewhat refractory with regard to these compounds, and whereas this refractoriness might be overcome by the use of large doses over long intervals, at present it seems wiser to change to another form of therapy. Radioactive iodine or surgical treatment is preferable for persons in whom it is not desirable to give prolonged treatment, especially in subjects who will not take a thiourea derivative regularly.

Thioureas or Radioactive Iodine.—Therapy with one of these compounds is desirable especially in the patients who cannot be gotten conveniently into satisfactory condition for thyroidectomy. They are useful in patients who cannot afford the extra expense of an operation and in those who have a great fear of such treatment. The use of one of the compounds is desirable in persons who have been subjected to one or more thyroidectomies and especially in those in whom a paralysis of the vocal cord has developed or in those with hypoparathyroidism.

Radioactive Iodine.—The use of radioactive iodine has the advantage over either of the other forms of therapy in its simplicity of administration and in its effectiveness in essentially all cases. It is distinctly less

expensive than surgical treatment and will become much cheaper, but it is available, thus far, to an extremely small number of patients. It is especially useful in patients who are unreasonable and difficult to manage. Moreover, it is probably the most certain way of abolishing thyrotoxicosis, although it is accompanied with a distinct risk of myxedema. The results thus far are promising and doubtless will improve greatly as more information is obtained about the regimen for optimal dosage. However, at present the results of this form of therapy are more uncontrollable than is true of either of the other types. The surgeon has much difficulty in deciding just how much of the thyroid tissue to leave in even when he has a good view of it. In the estimation of the amount of radioactive iodine to be used it is uncertain how much tissue is present and what the state is of iodine metabolism in the patient, both of which are factors of distinct importance in the determination of the optimal dosage. In general, it seems wiser to err on the side of not giving enough rather than of giving too much, because in the former instance additional doses can be administered. Even though a regimen of multiple dosage is used, it is still possible to overestimate the quantity of radioactive iodine that is necessary. If iodide or thiourea therapy has been given, it is important to discontinue the former four weeks and the latter one week before radioactive iodine is given. It is advisable to administer one of the thiourea compounds or potassium iodide, or both, during the period of approximately two months following treatment with radioactive iodine that is required to obtain a full effect. Hertz²² has found that when potassium iodide therapy is begun one day after the radioactive iodine has been given the latter is retained to a greater extent.

Two questions that are of concern with the isotopic therapy are not yet definitely answered: A. Will the gamma rays that are introduced be carcinogenic? Experiences with roentgenotherapy suggest that such an effect will be infrequent. B. What are the damaging effects to other portions of the body, especially the kidney? Another problem which may be presented in the future, with the utilization of the various isotopes in domestic activities, is the avoidance of excess radioactivity.

Thioureas.—This form of therapy would seem to offer more opportunity for development than would either of the other types, since many hundred compounds of this type remain unexplored. The rate of production of the thyroid hormone can be much more accurately controlled with thioureas than with surgical intervention or radioactive iodine. Therefore, the level of metabolism can temporarily be adjusted according to what is best for the patient. This regulative ability is sometimes desirable in persons with cardiac disease, anxiety neurosis

22. Hertz, S.: Personal communication to the author.

and malignant exophthalmos. This type of therapy is available to a larger group of persons than is either of the other types. It is useful in the preparation of patients for thyroidectomy and in those that are not cured by surgical treatment. It is indicated in patients who are waiting for radioactive iodine treatment and in those who are waiting for a response from the latter. It can be used advantageously when an insufficient amount of radioactive iodine has been given. Indeed, this combined type of therapy might well be superior to any of the other types of treatment. Surgical treatment or radioactive iodine always can be used after the thiourea therapy, if a change is desired. Therapy with thiouracil is more effective in patients with small goiters and slight thyrotoxicosis than in the severer cases. In some patients thyrotoxicosis is a self limited disease, and in these patients the thiourea derivatives not only can control the manifestations of the disease but may shorten its duration.

Comparison of Certain Thioureas and Aminobenzenes.—Now that many thioureas and aminobenzenes have been studied clinically²³ and many others have been shown to have pronounced antithyroid effects in rats,¹ the question arises what the relative values of these compounds are in the treatment of thyrotoxicosis.

On the basis of the study in this clinic of the comparative effects of many compounds, the following tentative order of decreasing potency may be given. As seen in table 4, there was no definite difference between the effects of 6-propylthiouracil and of 6-cyclopropylthiouracil, but each was more potent than were the other drugs. The next most active was 6-isobutylthiouracil, followed by 6-butylthiouracil, 6-methylthiouracil, thiouracil, ortho-phenylenethiourea, tetramethylthiourea, thiothymine and aminothiazole; last, and much less potent, was para-aminobenzoic acid. We have not had enough experience with thiourea to assess its relative value. Whereas 3, 5-diiodo-para-aminobenzoic acid was effective in some cases, it is difficult to determine how much of the effect was due to its iodine content. All the beneficial results obtained from the use of ethyldiiodobrassidate appeared to be due to the iodine. As far as the clinical application of the compounds is concerned, the order would be somewhat similar, except in the case of a few compounds which caused frequent toxic reactions, as, for example, ortho-phenylenethiourea and aminothiazole. For the same reason the use of thiobarbital is not as desirable.

23. (a) Leys, D.: Hyperthyroidism Treated with Methylthiouracil, *Lancet* **1**:461 (April 14) 1945. (b) Berman.¹² (c) Williams.¹⁰ (d) Astwood.¹⁴ (e) Bartels, E. C.: Use of Thiobarbital in the Treatment of Hyperthyroidism, *J. A. M. A.* **129**:932 (Dec. 1) 1945. (f) Astwood.¹⁵ (g) Perrault and Bovet.¹³ (h) Himsworth, H. P., and Morgans, M. E.: Aminothiazole in the Treatment of Thyrotoxicosis, *Lancet* **1**:800 (May 25) 1946. (i) Wilson, A.: Thyrotoxicosis Treated with Thiouracil and Methylthiouracil, *ibid.* **1**:640 (May 4) 1946.

Whereas Perrault and Bovet ¹³ were enthusiastic about aminothiazole, 11 per cent of their patients had toxic reactions. Of the patients whom we treated, severe arthritis, fever and rash developed in 1; in another patient hepatitis developed, but this was probably infectious in origin. Himsworth and Morgans ^{23h} obtained such unfavorable results in the treatment of 13 patients with aminothiazole that they discontinued this form of therapy.

Wilson ²³ⁱ compared the results of thiouracil treatment of 40 patients with the results of methylthiouracil therapy in 30 patients and obtained better results with the methyl derivative. Our experiences with this compound were also fairly satisfactory.

Although none of the toxic effects of ortho-phenylenethiourea was severe, consisting chiefly in fever, they were more frequent than was desirable. Thiothymine was not as active as were many other compounds, and it caused a moderately severe febrile reaction in 1 patient.

Whereas Berman ¹² was enthusiastic about the use of para-aminobenzoic acid, the response of his patients was extremely slow. Moreover, it is not practical to give almost daily intravenous injections for several months. Para-aminobenzoic acid was found not to exert much antithyroid effect when given orally in large doses. Indeed, it was not satisfactory in the maintenance of the normal metabolic rate which had been produced by thiourea derivatives. No synergistic effect of para-aminobenzoic acid with thioureas was observed in 2 patients in whom this was tested.

Tetramethylthiourea ¹⁰ was found to be a satisfactory drug, but its use occasionally caused a severe febrile reaction.

No significant toxic reactions were caused by 6-isobutylthiouracil, but it was replaced by the propyl derivatives whose antithyroid activity seemed to be greater.

Propylthiouracil and cyclopropylthiouracil appeared to be equally active, and neither drug caused any toxic reactions. Consequently, these drugs would seem to be the most desirable ones that are available at present.

In looking over the tables, especially table 4, the response of some of the patients to the "more potent" thiouracil derivatives can be observed to be slow. Indeed, in some of the cases a complete response is not shown in the table, but when iodide therapy supplemented the treatment with thiouracils, a complete remission was observed. Whether some of these patients would have shown a full response to a greater dosage of the thiouracils is unknown; some were receiving as much as 200 mg. daily. On the basis of the observations of the antithyroid effects of the propyl derivatives in rats, one would anticipate just as rapid a response in the patients with thyrotoxicosis treated with these compounds as in those treated with thiouracil, provided that an adequate

dosage is used. The relatively much greater activity of the propyl derivatives in rats has led to the use of smaller doses of these drugs than are really needed in some cases. By the use of doses slightly larger, toxic reactions might be produced, but this is not necessarily true. On the basis of pharmacologic studies which Kay and I have conducted,¹⁷ it would appear probable that even with the doses of the propyl derivatives which were used the concentrations of the drugs in the tissues were as great as or greater than those which exist with standard thiouracil therapy.

Whether a greater incidence of sustained remissions will follow therapy with the propyl derivatives than was true of thiouracil therapy remains to be determined. However, there is no good reason for assuming this at present, since the mechanism of action of the two compounds is probably similar.

SUMMARY AND CONCLUSIONS

A total of 112 thyrotoxic patients have been given two hundred and twenty-two courses of therapy with some of the newer antithyroid drugs. Many of these patients were treated with several courses of therapy, a different compound being used each time, and comparisons were made of the effectiveness of the drugs in the same and in different patients. The strongest antithyroid action was shown by 6-propylthiouracil and 6-cyclopropylthiouracil. The other drugs, in order of decreasing potency were: 6-isobutylthiouracil, 6-butylthiouracil, 6-methylthiouracil, ortho-phenylenethiourea, thiothymine and aminothiazole. Thiouracil could be placed immediately after 6-methylthiouracil and tetramethylthiourea after ortho-phenylenethiourea in the order of potency. The order of desirability of the drugs is somewhat the same as their order of potency, with the exception of ortho-phenylenethiourea, which caused toxic reactions more frequently than did the other drugs. The use of aminothiazole caused severe arthritis, dermatitis and fever in 1 patient. In 58 patients treated with 6-cyclopropylthiouracil and in 39 treated with 6-propylthiouracil no toxic reactions were observed. In 43 patients treated with 6-isobutylthiouracil the only toxic reaction was slight itching in a few patients.

Para-aminobenzoic acid was not notably active even when given in large doses. On the other hand, the use of 3, 5-diiodo-para-aminobenzoic acid produced a rapid response in a few patients. Whether the favorable results were due to a decided affinity of the thyroid for iodine, thereby leading to a concentration of the aminobenzene radical in the thyroid, or whether they were due to the regular effect of iodine is not known, although the rapidity of response and of relapse in spite of continuous therapy was more suggestive of the latter. The action of the orthoamino analogue was somewhat similar.

Ethyldiiodobrassidate, an iodinated fatty acid derivative, was not definitely superior to potassium iodide, even when given intramuscularly as well as orally.

A discussion is given of the relative merits of radioactive iodine, subtotal thyroidectomy and thioureas in the treatment of thyrotoxicosis. It is concluded that the individual circumstance may determine the treatment of choice, although there are many cases in which the decision is optional and may depend on a number of factors as, for example, the temperament of the patient. Indeed, in some instances the decision is difficult, but it should become easier as more is learned about the chronic effects of radioactive iodine and of the thioureas. Thiourea derivatives can be used effectively in conjunction with radioactive treatment, or vice versa. It is sometimes of advantage to use all three forms of therapy.

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THIOURACILS AND THIOUREAS

Comparisons of the Absorption, Distribution, Destruction and Excretion

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IN THE ATTEMPT to obtain antithyroid compounds which were superior to 2-thiouracil, it seemed important not only to test the thyroid-inhibiting effects of many related substances in animals¹ but also to compare the activities of the more potent goitrogenic compounds in patients with thyrotoxicosis.² Moreover, it was regarded as important

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to investigate the differences in the manner in which the body handles these drugs, especially as regards their absorption, distribution, destruction and excretion. Studies of this nature have previously been made with thiouracil,³ thiourea,⁴ diethylthiourea,^{2c} tetramethylthiourea^{2c} and aminothiazole.^{2g} All these drugs are rapidly absorbed from the gastrointestinal tract and destroyed in the body. None of the first four compounds is excreted in the stools; approximately one third of these substances is excreted in the urine. In the case of thiouracil, which has been studied more extensively than the other compounds, the following significant observations have been made.⁵

1. Accurate estimations can be made of its concentrations in all the tissues and fluids of the body.

2. It is rapidly absorbed from the gastrointestinal tract, significant concentrations in the blood developing within fifteen minutes, but about 15 per cent of the drug is destroyed in the gastrointestinal tract. The secretions of the stomach, duodenum and jejunum, but not the contents of the ileum, possess the capacity to break down the drug.

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5. (a) Williams, Kay and Jandorf.^{3a} (b) Williams.^{3b} (c) Williams.^{2c}

3. Most of the thiouracil in the blood is in the cells, and nearly all of it is bound to protein. It can be freed from the protein by digestion with trypsin; it has been released from serum by ultrafiltration at a low p_H .⁶ The concentration of thiouracil in the blood rarely exceeds 6 mg. per hundred cubic centimeters, regardless of dosage, damage to the kidney or hepatic damage.

4. It has been found in essentially all the tissues and fluids of the body, but the concentrations have been different.

5. Approximately one half of the total amount of thiouracil ingested is broken down in the body, essentially all tissues possessing this capacity to varying degrees.

6. About one third of the drug ingested is excreted unchanged in the urine. The products of disintegration of thiouracil have not been established, but following its administration there is an increased excretion in the urine of neutral sulfur.

7. Thiouracil is transported through the placenta in biologically active quantities.

In the studies of other thiouracils reported in this paper not so many phases of action were investigated as were done with thiouracil, but certain comparative studies were made of thiothymine (5-methylthiouracil), ortho-phenylenethiourea and several thiouracils possessing hydrocarbon chains as substituents in the 6-position: methyl, ethyl, n-propyl, cyclopropyl, n-butyl, isobutyl and amyl groups.

METHODS

In 1943 methods for the determination of thiouracil in any of the tissues and fluids of the body were worked out.⁷ These methods have now been used satisfactorily in this laboratory for several thousand determinations and have been applicable to a wide variety of concentrations of many thioureas and thiouracils. The methods depend on the production of a blue or green color when these compounds are mixed with Grote's reagent. This reagent is made by the addition of sodium nitroferricyanide, hydroxylamine hydrochloride and sodium bicarbonate to distilled water; bromine is added to this solution. Several points require special consideration: 1. Most of the thiouracils are not readily soluble in acid solution. 2. A large proportion of each thiourea compound in the blood is bound to protein and must be freed. 3. The amount of bromine in Grote's reagent must be accurately controlled. 4. The factors of time and p_H are extremely important. Moreover, it is to be borne in mind that certain bacteria or pronounced heat may alter the thiouracil molecule.

6. Christensen, H. N.: Ultrafiltrability of Thiouracil in Human Serum: Determination of Thiouracil, *J. Biol. Chem.* **160**:425 (Oct.) 1945.

7. Williams, R. H.; Jandorf, B. J., and Kay, G. A.: Methods for the Determination of Thiouracil in Tissues and Body Fluids, *J. Lab. & Clin. Med.* **29**:329 (March) 1944.

Precipitation of Proteins.—For the precipitation of the proteins several common protein precipitants were tried. It was desirable to precipitate the proteins at an alkaline p_H because the thiouracils are much more soluble than at an acid p_H . For example, at p_H 3.2 less than 50 mg. of thiouracil was soluble in 100 cc. of water at 25 C. This concentration of the drug was exceeded in certain of the studies reported in this paper, as well as in others. Moreover, even with concentrations of thiouracil in which there is no problem of solubility our recoveries from the blood of patients treated with the drug are not as good when trichloroacetic acid is used as the protein precipitant as when cadmium chloride is used. For example, with the use of the latter precipitant 1 patient was found to have 3.8 mg. of thiouracil per hundred cubic centimeters of blood. With precipitation with trichloroacetic acid, as described by Christensen,⁶ only 53 per cent of this amount was found; with tryptic digestion preceding the precipitation with trichloroacetic acid, 64 per cent was demonstrated. That a falsely high value was not obtained with the cadmium chloride was shown by recovering approximately 100 per cent of the compound when thiouracil was added to the blood of the untreated patient.

In order to obtain alkaline filtrates, a mixture of sodium tungstate and copper sulfate was tried. However, one handicap with this method of precipitation was that unless the p_H was carefully regulated copper ions would appear in the filtrate, giving a blue color which interfered with the colorimetric estimations. To improve this step several other protein precipitants were tried. Alcohol was used⁸ but was unsatisfactory because a red filtrate was obtained. However, cadmium chloride was found to be satisfactory. To 1 cc. of blood was added 9 cc. of a 1 per cent solution of cadmium chloride and 1 cc. of normal sodium hydroxide. It was desirable to centrifuge the mixture in order to hasten the rate of filtration, since the precipitate is extremely heavy. Grote's reagent was found to yield a precipitate with the excess cadmium chloride in the precipitate, probably forming cadmium ferricyanide. When sodium carbonate was added, a flocculent precipitate was formed which could be readily separated by filtration. When Grote's reagent was added to this filtrate, containing thiouracil, a clear green color developed. Since the p_H of the filtrate following precipitation with sodium carbonate was in the range of 11.0, necessitating adjustment to about 8.5, barium carbonate was tried as a substitute for the sodium carbonate, since it did not produce as much elevation in the p_H , but it did not cause adequate precipitation of the cadmium.

A satisfactory precipitation was not obtained when sodium carbonate was added at the same time as the cadmium chloride and sodium hydroxide, probably because of the elevation of the p_H . Therefore, in summary, the following procedure is used:

1. To 1 cc. of blood is added 9 cc. of 1 per cent cadmium chloride and 1 cc. of normal sodium hydroxide.
2. The mixture is shaken, centrifuged and filtered.
3. To the filtrate is added a knife edge of solid sodium carbonate. This is shaken and filtered.
4. The p_H of the filtrate is adjusted to a range of 8 to 9, and then the procedure is the same as the one previously described.

The foregoing method is applicable to tissue. It is important not only to add sodium hydroxide but also to let the mixture stand for several hours. That

8. Hiller, A., and Van Slyke, D. D.: A Study of Certain Protein Precipitants, *J. Biol. Chem.* **53**:253 (Aug.) 1922.

sodium hydroxide aids in the release of thiouracil from the tissues was shown on analyzing muscles of rats treated for several days. However, tryptic digestion is necessary to insure complete release of the thiouracil.

Bromine in Grote's Reagent.—In view of the fact that thiourea and thiouracil react with iodine, it was thought probable that a similar reaction would take place with bromine and would, therefore, be of great concern if any excess bromine were in Grote's reagent. If too little bromine is used in Grote's reagent, a cloudy solution is obtained, but when there is too much bromine there is a reddish color instead of a mahogany one. To 100 cc. of solution of 20 mg. of thiouracil per hundred cubic centimeters was added 1 drop of bromine. The mixture was permitted to stand for fifteen minutes and then assayed for thiouracil in the usual manner; only 14 per cent of the thiouracil was recovered. Therefore, it is most important to get rid of the excess bromine, and, furthermore, it is imperative that each new batch of Grote's reagent be tested with a standard solution of thiouracil. Phenol has been used to get rid of the excess bromine, but this sometimes causes a precipitate to form.

Properties of Thioureas and Thiouracils Tested.—All the antithyroid drugs studied, listed previously, tended to be somewhat insoluble in water but were

TABLE 1.—Accuracy of Determinations of Thiouracils in Blood, Tissue and Urine

Concentrations tested, mg./100 cc.	Blood				Tissue Suspension					Urine			
	0.4	1.6	2.4	4.0	0.5	1.0	5.0	8.0	10.0	1.0	4.0	10.0	20.0
	% Recovered												
6-Methylthiouracil.....	100	91	100	100	100	90	100	98	100	100	100	100	100
6-Ethylthiouracil.....	100	100	100	95	100	100	96	98	100	100	100	100	100
6-Propylthiouracil.....	100	100	100	100	100	100	100	100	100	100	100	100	100
6-Cyclopropylthiouracil.....	100	100	100	88	0	0	80	63	60	0	0	24	58
6-Butylthiouracil.....	100	100	100	95	100	80	100	100	100	100	100	100	100
6-Isobutylthiouracil.....	0	87	83	100	0	50	60	87	80	60	75	80	90
6-Amylthiouracil.....	100	100	100	100	100	80	96	100	100	100	100	100	100

soluble in an alkaline medium. Thiouracil and ortho-phenylenethiourea were the most insoluble. The maximal color reaction of each compound was transmitted at a wavelength of 660, with the exception of 6-hexylthiouracil, which was at 550. When plotted on semilogarithmic paper, a straight line relationship was found to exist between the concentration and the intensity of color for each of the compounds. The maximal development of color took place in fifteen minutes, and the color was stable for one hour. The color formed by ortho-phenylenethiourea faded more rapidly than did the others.

Recoveries from Blood, Tissues and Urine.—Excellent recoveries from blood, tissues and urine were obtained (table 1) with the following thiouracil derivatives: 6-methyl, 6-ethyl, 6-propyl, 6-butyl, 6-amyl and 6-hexyl. The recoveries of 6-cyclopropylthiouracil were good in the blood but poor in tissue suspension or in urine. The recoveries of ortho-phenylenethiourea from blood and urine were poor. Isobutylthiouracil was incompletely recovered from the blood, tissues and urine. Christensen⁹ has also obtained good recoveries when certain thiouracils were added to serum. However, the poor recoveries which he obtained with 6-hexyl-

9. Christensen, H. N.: Analytical Determination and Some Properties of Several Thyroid-Inhibiting Compounds and of Substances Related to Them, J. Biol. Chem. **162**:27 (Jan.) 1946.

thiouracil were contrary to our experience. For example, with the following concentrations of this compound—0.4, 0.8, 1.6, 3.2 and 4.0 mg. per hundred cubic centimeters of whole blood—the per cent recoveries were respectively 100, 75, 100, 94 and 90.

Preservatives for Urine.—Various preservatives were used in urine before a satisfactory one was found. Whereas chloroform is a good preservative, it extracts a small amount of thiouracil; toluene extracts a good deal. Sodium fluoride or thymol did not offer this problem, but they did not always inhibit bacterial growth. Acids were used satisfactorily, but they necessitated adjustment of the pH . Thus far the addition of 5 cc. of 40 per cent formaldehyde per twenty-four hour specimen of urine has been satisfactory.

RESULTS

Rate of Breakdown of Propylthiouracil as Compared with Thiouracil.
—Fifteen male rats, weighing about 130 Gm., were given 5 mg. of 6-propylthiouracil each intravenously¹⁰ and killed, in groups of three,

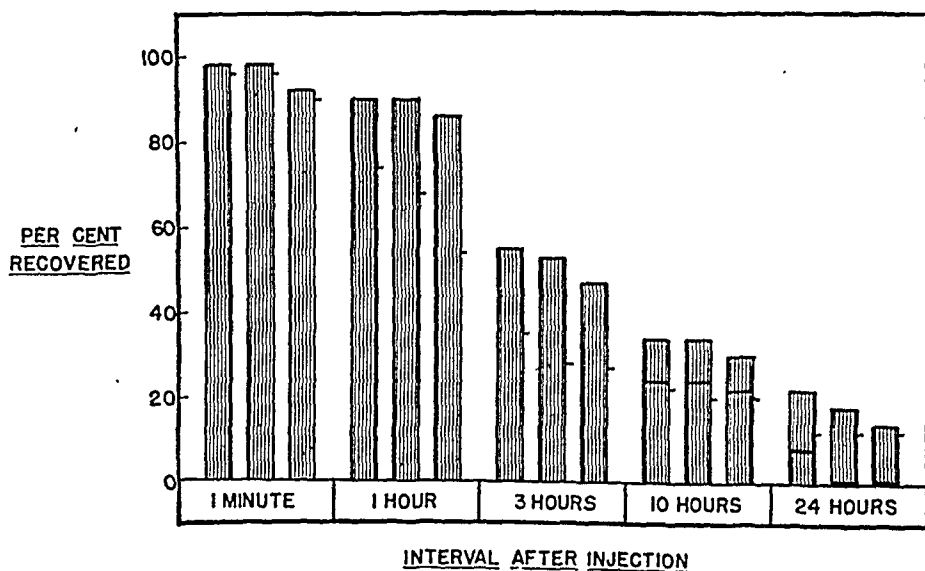


Chart 1.—Rate of destruction of propylthiouracil in the body. Each column indicates the proportion of 6-propylthiouracil remaining in the body of 1 rat after the injection, intravenously, of 5 mg. of this compound. The portion of the column above the crossbars represents the amount of the drug excreted in the urine. The side arms are values for thiouracil in another experiment conducted in an identical manner; they include the thiouracil in the urine of the rats killed after ten and twenty-four hours. Each rat weighed approximately 130 Gm.

after one minute, one hour, three hours, ten hours and twenty-four hours. All urine was saved and analyzed. An identical experiment was conducted with thiouracil. That accurate analyses of the whole animals could be conducted was demonstrated by recovering nearly 100 per cent of the compound from animals that were killed one minute after the injections. It can be observed in chart 1 that a rapid rate of destruction occurred with each compound, being faster with thiouracil than with

10. All the thiouracils injected intravenously were in the form of their sodium salt.

6-propylthiouracil. After ten hours only about 23 per cent of 6-propylthiouracil and 15 per cent of thiouracil remained in the carcass. After twenty-four hours there was none of the latter and little of the former; about 15 per cent of thiouracil was excreted in the urine.

Concentration in the Body and Thyroid Gland of Thiouracils Injected Intravenously.—Rats weighing about 130 Gm. received injections into the femoral vein of 5 mg. of thiouracil or one of its derivatives possessing one of the following radicals in the 6-position: methyl, ethyl, propyl, butyl or amyl. Six rats were given injections of one compound; 3 of these were killed after one minute, and the total amount of drug in the body was determined. As shown in chart 2, about 90 per cent or more of the compound injected was recovered; therefore, the method was

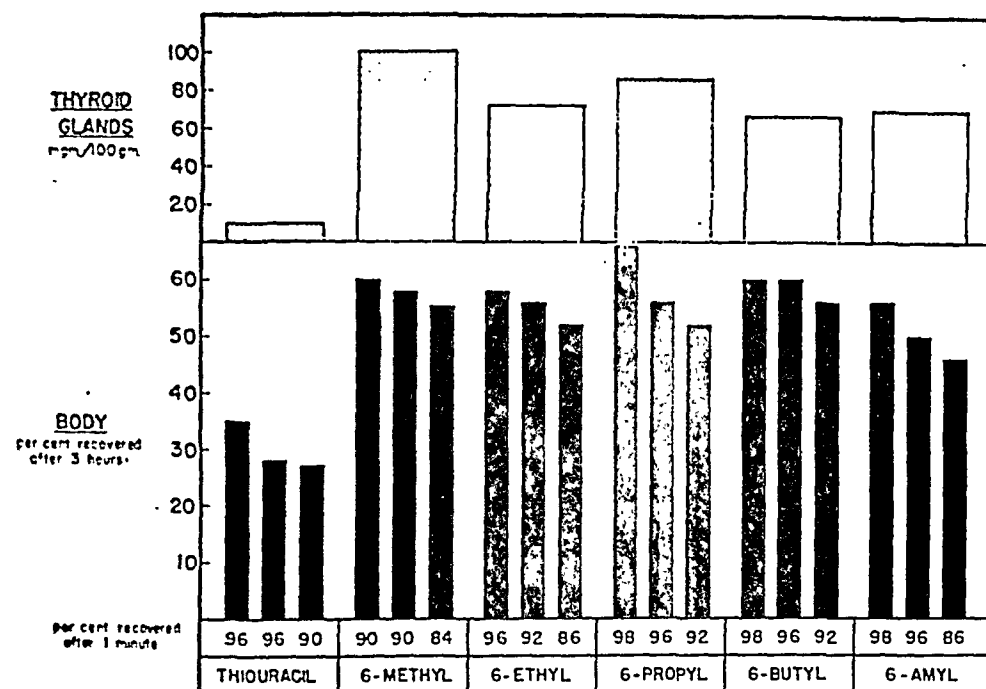


Chart 2.—Concentration of thiouracils after intravenous administration of 5 mg. Each narrow column represents the proportion of thiouracil or one of its derivatives remaining in the carcass of 1 rat three hours after the intravenous injection of 5 mg. of one of the compounds. The broad columns represent the amount of drug found in pooled specimens of three thyroid glands. At the bottom of the chart the accuracy of the determinations is indicated by the high percentage of recovery of the compounds in rats that were killed one minute after the substances had been injected. Each rat weighed about 130 Gm.

considered satisfactory. The other rats were killed three hours after injection, and an analysis was made for the total amount of thiouracil in the body and in a pooled specimen of three thyroid glands. As can be observed in chart 2, there was a decidedly smaller quantity of the drug found in the body and in the thyroid gland in the case of thiouracil than was true of its derivatives. There was no noteworthy difference between the concentrations of the various derivatives.

Concentration in the Body and Thyroid Glands of Ingested Thiouracils.—To each of twelve groups of rats, with 3 rats per group, was given thiouracil or one of its derivatives. These compounds were given as 0.02 per cent or 0.05 per cent solutions, each group of 3 rats receiving 36 cc. per day as their intake of fluid. After five days the animals were killed, and estimations were made of the concentration of drug in the body and in the thyroid gland. These rats weighed about 105 Gm. each.

In the body of the animals that received the 0.05 per cent solution, or a total of 90 mg. for 3 animals, of one compound or another there was about three times as much 6-methyl, 6-propyl and 6-amyl thiouracil as there was of thiouracil, as shown in chart 3. There was slightly more

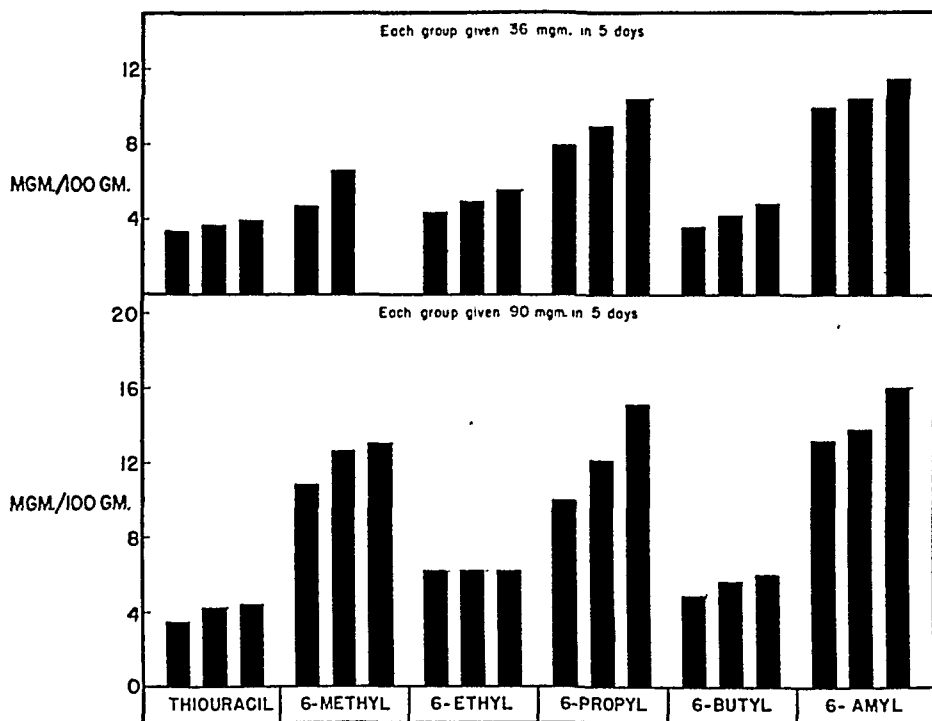


Chart 3.—Concentration of thiouracils in body. Each column indicates the concentration of thiouracil or one of its derivatives in the body of 1 rat. The results in the top of the chart are of experiments on animals, each 3 of which were given 36 cc. of a 0.02 per cent solution of one of the compounds. This amount was given as their daily drinking water. The results in the lower half of the chart are of experiments on rats, each 3 of which were given daily 36 cc. of a 0.05 per cent solution of the respective compounds. Each rat weighed approximately 105 Gm.

6-ethyl and 6-butyl thiouracil than there was of the parent compound. It is striking that the derivatives with an odd number of carbon atoms in the 6-position are much more concentrated than are those with an even number.

All the substituted thiouracils were found in the thyroid gland in greater concentration than was thiouracil itself, as seen in chart 4. It

was surprising to note that the three derivatives of thiouracil existing in greatest concentration in the body as a whole were less concentrated in the thyroid than were the two other derivatives. The ratio of drug in the thyroid to that in the body was much greater in the case of 6-ethyl and 6-butyl thiouracil than was true of the other compounds, as seen in table 2; it was least in the case of 6-propylthiouracil.

In the body of the animals receiving 36 mg. of the drugs there was a great deal less concentration of the compounds than was found in those receiving 90 mg., but the same relative comparisons existed, except that there was not quite as great a proportionate excess of the 6-methyl, 6-propyl or 6-amyl derivatives, as shown in chart 3. The concentrations of the compounds in the thyroids were in the same relative order as in the animals receiving 90 mg. in five days, as seen in chart 4.

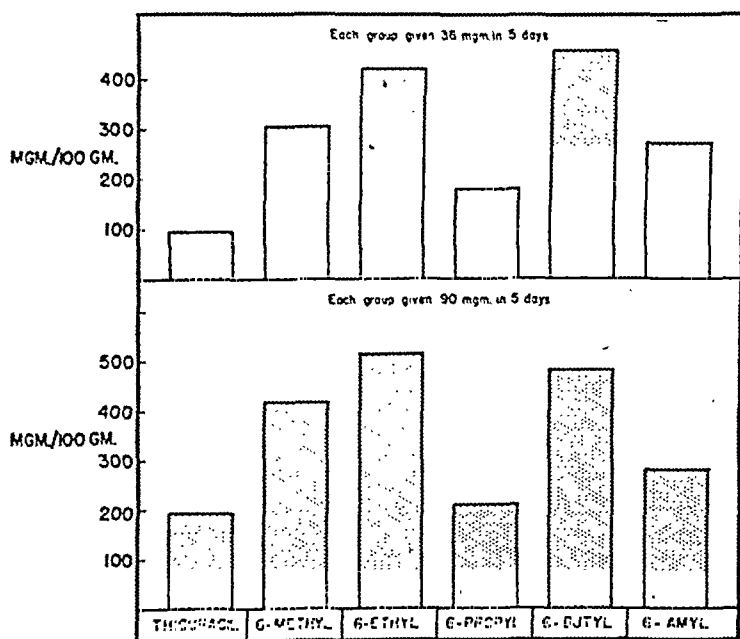


Chart 4.—Concentration of thiouracils in thyroid glands. Each column represents the concentration of the thiouracils in a pooled specimen of three thyroid glands, corresponding to the carcasses in chart 3.

Studies identical to the foregoing were carried out with 6-isobutylthiouracil, but the results are not included in the charts, since only incomplete recoveries could be obtained with this compound; in spite of this fact, a larger quantity of isobutylthiouracil was found in the body and thyroids of these animals than was the case with thiouracil.

Two further experiments were conducted, similar to the foregoing ones except that the animals were permitted to have for their intake of fluid as much 0.05 per cent thiouracil or 6-propylthiouracil as they desired. That the body was not saturated with these compounds in two days is shown by the fact that the concentration in the carcass and in the thyroid gland was many times higher at the end of five days,

as shown in table 3. In a comparison of the results in table 3 with those in charts 3 and 4, it can be seen that the concentration of either thiouracil or 6-propylthiouracil was much greater when 0.02 per cent solution was given for five days than when 0.05 per cent was given for two days. It can also be seen in table 3 that in comparison with the amount of drug ingested the concentration of 6-propylthiouracil is greater than that of thiouracil, in the thyroid as well as in the body.

Concentrations of Thiouracils in the Blood of Human Beings.—On the basis of many studies with thiouracil it was concluded that in study-

TABLE 2.—*Ratio of Concentration of Thiouracils in the Thyroid to That in the Body*

Amount ingested in five days.....	90 mg.	36 mg.
	Concentration in Thyroid : Body	
Thiouracil.....	48	31
6-Methylthiouracil.....	34	54
6-Ethylthiouracil.....	84	86
6-Propylthiouracil.....	17	20
6-Butylthiouracil.....	86	109
6-Amylthiouracil.....	20	26

TABLE 3.—*Thiouracil and Propylthiouracil in Body and Thyroid*

Drug	Dura- tion of Ingestion, Days	Total Drugs* Ingested by Three Rats, Mg.	Total Drug in Carcass,† Mg.	Weight of Thyroid, Mg.	Drug in Thyroids ‡	
					Total, Mg.	Mg./100 Gm.
Thiouracil.....	2	41	1.2 1.3 1.2	44.5	0.008	17.7
6-Propylthiouracil.....	2	31	2.5 2.1 2.5	41.9	0.01	23.8
Thiouracil.....	5	163.5	6.2 7.6 6.6	47.1	0.07	148.6
6-Propylthiouracil.....	5	105	15.9 11.2 11.5	52.9	0.06	113.4

* Given in the drinking water in the form of a 0.05 per cent solution.

† Each rat weighed approximately 180 Gm.

‡ The thyroid glands were analyzed in groups of three; the carcasses were analyzed singly.

ing the derivatives of this compound a good indication of the changes in concentration within the blood could be obtained with analyses of blood made immediately before a given dosage, thirty minutes thereafter and two hours after the drug was administered. These studies were made only after the patient had taken the specified drugs, listed in table 4, for more than three days.

It can be seen that the concentrations of 6-propylthiouracil were somewhat higher than those of thiouracil when more than 100 mg. daily was given; there were no essential differences with dosages less than this. When either drug was given in doses of only 50 mg., none of either compound was found immediately preceding or two hours after administration of the drug. These studies were made only after the patient had taken the specified drugs, listed in table 4, for more than three days.

The patients receiving 6-cyclopropylthiouracil maintained a higher concentration in the blood than did the ones receiving either thiouracil or 6-propylthiouracil. The content of 6-methylthiouracil and thiothymine (5-methylthiouracil) was less than that of the propyl derivatives. The concentration of ortho-phenylene-thiourea was greater than that of any of the others tested, in spite of the fact that the recovery of this compound from blood was poor.

TABLE 5.—*Distribution of Thiouracils in Blood*

Drug	Daily Dosage, Mg.	Mg. per 100 Cc. of Blood			Hematocrit Reading
		Whole Blood	Plasma	Blood Cells	
Thiouracil.....	1,000	2.3	0.3	2.0	29
Thiouracil.....	150	0.4	0.0	0.3	42
6-Propylthiouracil.....	600	1.8	0.4	1.3	35.5
6-Propylthiouracil.....	150	1.0	0.3	0.6	36
6-Cyclopropylthiouracil.....	150	1.4	0.3	1.0	45

The distribution of 6-propylthiouracil and 6-cyclopropylthiouracil resembles that of thiouracil in that most of the drug exists in the blood cells, as seen in table 5.

Thiouracil in the Tissues of a Patient with Thyrotoxicosis.—In a previous report values were given for the concentration of thiouracil in essentially all the tissues and fluids of the body, but these specimens were taken chiefly from patients who had been sick for several days preceding death. Recently, however, we were afforded an opportunity to examine the tissues of a patient who had been treated with thiouracil for thyrotoxicosis but who died instantly. According to a résumé which was kindly supplied by Dr. Ruth Towne, the patient was a Negro woman, aged 26, with a history of thyrotoxicosis for a period of eleven months. She presented the picture of fairly severe exophthalmic goiter. The only unusual feature about the case was that occasionally she had complete heart block, with a pulse rate of about 40 beats per minute. She was treated with strong solution of iodine U. S. P. for nineteen days, after which she had no antithyroid treatment for seven days, and then she was given 0.1 Gm. of thiouracil three times daily. Although she improved under this treatment, she was still somewhat thyrotoxic

until death. After receiving treatment with thiouracil for eleven days, she died instantly in association with panic provoked by her baby's attempt to crawl out of a window. Since the autopsy was not performed until about eighteen hours after death, there was an opportunity for some of the thiouracil to be broken down.

The tissues containing the largest concentrations of thiouracil were adrenal, ovary, spleen and liver, as shown in table 6. All these tissues

TABLE 6.—*Thiouracil in Tissues and Fluids of a Subject with Thyrotoxicosis*

Tissue	Amount of Thiouracil	
	Mg./100 Gm. Wet Weight	Mg./100 Gm. Dry Weight
Thyroid.....	0.9	2.8
Pancreas.....	0.9	3.4
Adrenal.....	2.7	12.1
Ovary.....	2.1	5.4
Thymus.....	0.6	1.0
Breast.....	0.0	0.0
Skin.....	0.0	0.0
Muscle.....	0.0	0.0
Heart.....	0.0	0.0
Lung.....	0.4	0.9
Spleen.....	3.4	6.2
Liver.....	2.1	8.9
Kidney.....	0.9	7.2
Lymph node.....	0.0	0.0
Bone marrow.....	1.2	16.0
Blood.....	1.0	11.2
Bile.....	0.0	0.0
Cerebrospinal fluid.....	1.4	116.0

TABLE 7.—*Thiouracils in Urine*

Dose of thiouracils.....	50 mg.	50 mg.	50 mg.	100 mg.	100 mg.	200 mg.	200 mg.
Times daily.....	1	2	3	2	3	2	3
Thiouracil							
Average mg./day.....	26	8	29	80	50	133	203
Specimens.....	3	3	3	14	4	17	17
6-Propylthiouracil							
Average mg./day.....	25	13	15	..	21	16	81
Specimens.....	3	3	6	..	3	4	3
6-Methylthiouracil							
Average mg./day.....	106	92
Specimens.....	4	7
Thiothymine							
Average mg./day.....	19	27	...	67
Specimens.....	2	5	...	20

had a greater concentration of the drug than did the blood. No thiouracil was found in the skin, breast, muscle, heart, lymph nodes or bile.

Amount of Thiouracils in the Urine.—After certain patients had been taking one of the thiouracils for more than three days, urine was collected for intervals of twenty-four hours, and the total amount of the drug was estimated. In general, about one third or less of the drug ingested was excreted in the urine. It can be seen in table 7 that

with the higher range of doses a relatively smaller amount of 6-propylthiouracil or thiothymine was excreted than was true of thiouracil or 6-methylthiouracil.

COMMENT

The mechanism of action of the thiouracils is reasonably conceivable as being due either to (a) an inhibitory effect on the activity of an oxidase in the thyroid gland, thereby interfering with the release of free iodine which, in turn, is necessary for the iodination of tyrosine, or (b) to a reaction of the thiouracils with iodine to form a disulfide of thiouracil and an iodide salt or (c) to both of these phenomena. In view of these possibilities, the concentration of a thiouracil in the thyroid gland would seem to have a significant influence on the antithyroid activity of the compound. Consequently, the effectiveness would appear to be influenced by the rate of absorption, breakdown and excretion of the drug, as well as the affinity of the thyroid to hold it. Such factors as the capacity of the compound to react with iodine and combine with protein might also be of significance. Many of the factors just mentioned probably are also concerned with the frequency and severity of toxic reactions to thiouracils.

Although thiourea, thiouracil and related compounds have been shown to react with iodine¹¹ and possibly by such a mechanism deprive the thyroid of iodine, the degree of antithyroid activity is not proportional to their reactivity with iodine when the latter is based on in vitro experiments. Moreover, in vivo there are a number of variable factors affecting this reaction. In the first place, in order for the reaction to occur the iodine must be in its free, or oxidized, form; thiouracil does not react with iodide. The iodine in the blood is presumably in the form of iodide, being changed to free iodine in the thyroid gland, possibly by the action of an oxidase. If by chance the thiouracils completely block the action of this enzyme, there would not seem to be a necessity for these drugs to react with iodine. By the inhibition of the oxidase activity, the production of iodine from iodide would be antagonized and there would conceivably be little free iodine for the thiouracil to react with. Miller and his associates¹¹ found that 6-aminothiouracil was about as reactive with iodine as was thiouracil, yet the antithyroid activity of the latter was a thousand times as great. This observation can be interpreted as an indication that the activity of the compounds is more dependent on their inhibitory effect on oxidase activity than on the capacity to react with iodine. As a test for this hypothesis, the capacity of 6-aminothiouracil and thiouracil to inhibit the action of horseradish peroxidase was studied in this laboratory, a modification

11. Miller, W. H.; Roblin, R. O., Jr., and Astwood, E. B.: Studies in Chemotherapy: XI. Oxidation of 2-Thiouracil and Related Compounds by Iodine, J. Am. Chem. Soc. **67**:2201 (Dec.) 1945.

of the method of Bancroft and Elliott¹² being used. The results indicated that both compounds cause partial inhibition of activity of this enzyme. The applicability of these observations to enzymes of the thyroid gland is uncertain.

Thiouracils combine with the proteins of the serum to varying degrees, but there does not seem to be any correlation of this reaction with the amount of antithyroid action.

Of the thiouracils studied, the derivatives accumulated in the body in greater concentration than did thiouracil. Moreover, the derivatives had a stronger antithyroid action than did the parent substance, but the antithyroid activity of the various compounds was not proportional to their concentration in the body or in the thyroid gland. In this connection, it should be pointed out that in a study of many patients treated with thiouracil¹³ there was no proportionate relationship of the content of thiouracil in the thyroid gland to the clinical response of the thyrotoxicosis. Furthermore, the concentration of thiouracils in the blood has not been associated with the amount of action in the thyroid gland. Therefore, the degree to which the compounds are stored in the thyroid is not the all-important factor in the determination of the amount of thyroid-inhibiting effect. Such factors as the intracellular distribution of the compound and the specific reactivity of the latter are doubtless of great significance.

SUMMARY

The method used for the determination of thiouracil has been successfully applied in the estimation of the rate of absorption, distribution, destruction and excretion of several of the most active antithyroid compounds.

The rate of breakdown of thiouracil was more rapid than of its derivatives with substituents in the 6-position: methyl, ethyl, propyl, butyl or amyl. These derivatives accumulated in the body, and thyroid gland of rats in much greater quantities than did thiouracil. Derivatives with an odd number of carbon atoms accumulated in the body in greatest amounts, but the largest concentrations in the thyroid gland occurred with derivatives bearing an even number of carbon atoms, namely, ethyl and butyl. In the case of all the compounds tested the concentration in the thyroid was many times greater than that in the body. There was no definite correlation of the amount of drug in the thyroid with its antithyroid activity.

12. Bancroft, G., and Elliott, K. A. C.: The Distribution of Peroxidase in Animal Tissues, *Biochem. J.* **28**:1911, 1934.

13. Williams, R. H., and Clute, H. M.: Thiouracil in the Treatment of Thyrotoxicosis, *J. A. M. A.* **128**:65 (May 12) 1945.

In patients receiving more than 100 mg. of 6-propylthiouracil daily the concentration of this compound in the blood was greater than that of thiouracil given in equivalent doses; there was no essential difference when the daily dosage was less than 100 mg. When either drug was given in doses of 50 mg. once daily, only a small amount was found in the blood after thirty minutes and none after two hours. Patients treated with 6-cyclopropylthiouracil were found to have a higher concentration in the blood than did those treated with 6-propylthiouracil or thiouracil. The concentration of ortho-phenylenethiourea was greater than that of the other compounds tested. Most of the 6-propylthiouracil and 6-cyclopropylthiouracil in the blood, like thiouracil, exists in the cells.

In a patient treated with thiouracil who died instantly the amount of the drug was found to vary a great deal in the tissues and fluids. The greatest concentrations were in the adrenals, ovaries, spleen and liver. The concentration in the thyroid gland was similar to that in the blood.

Roughly one third of the compounds was excreted in the urine.

STREPTOBACILLUS MONILIFORMIS BACTEREMIA WITH MINOR CLINICAL MANIFESTATIONS

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TWO ETIOLOGIC agents for rat bite fever have been described¹—*Spirillum minus* and *Streptobacillus moniliformis*.

The clinical picture can be caused not only by the bites of rats and other animals² but by the ingestion of infectious material. The Haverhill outbreak of 1926 illustrates the latter mode of infection. In 86 cases reported by Place, Sutton and Willner³ the disease was traced to the ingestion of unpasteurized milk and ice cream from a single source. Parker and Hudson⁴ isolated *Str. moniliformis* from the blood in 11 of these cases. In their review, Brown and Nunemaker^{1d} further stressed the frequency of *Str. moniliformis* as the etiologic agent in rat bite fever.

Treatment of this disease, until recent years, was limited to the use of arsenicals, gold salts and sulfonamide compounds. The last two have been of no value. The use of neoarsphenamine and oxophenarsine hydrochloride has given apparently satisfactory results in infections with *S. minus* but has been unsatisfactory in cases of infection with *Str.*

From the Division of Bacteriology of the Laboratories and the First Medical Service, the Mount Sinai Hospital, New York.

1. (a) Futaki, K.; Takaki, I.; Taniguchi, T., and Osumi, S.: *Spirochaeta Morsus Muris*: The Cause of Rat Bite Fever, *J. Exper. Med.* **25**:33 (Jan.) 1917. (b) Bayne-Jones, S.: Rat Bite Fever in the U. S., *Internat. Clin.* **3**:235 (Sept.) 1931. (c) Litterer, W.: A New Species of *Streptothrix* Isolated from a Case of Rat Bite Fever, *J. Tennessee M. A.* **10**:310 (Dec.) 1917. (d) Brown, T. McP., and Nunemaker, J. C.: Rat Bite Fever, *Bull. Johns Hopkins Hosp.* **70**:201 (March) 1942.

2. Dick, G. F., and Tunnicliff, R.: A *Streptothrix* Isolated from the Blood of a Patient Bitten by a Weasel, *J. Infect. Dis.* **23**:183 (Aug.) 1918. Mock, H. E., and Morrow, A. R.: Rat Bite Fever Transmitted by Cat Bite, *Illinois M. J.* **61**:67 (Jan.) 1932.

3. Place, E. H.; Sutton, L. E., and Willner, O.: *Erythema Arthriticum Epidemicum*: Preliminary Report, *Boston M. & S. J.* **194**:285 (Feb. 18) 1926. Place, E. H., and Sutton, L. E.: *Erythema Arthriticum Epidemicum* (Haverhill Fever), *Arch. Int. Med.* **54**:649 (Nov.) 1934.

4. Parker, F., Jr., and Hudson, N. P.: The Etiology of Haverhill Fever, *Am. J. Path.* **2**:357 (Sept.) 1926.

moniliformis. In recent years penicillin has been used with good results, both clinically⁵ and experimentally,⁶ in infections with the latter organism.

The case presented here is unusual in that the clinical picture was not the outstanding feature. Inasmuch as symptoms were few, the observations of principal interest were bacteriologic. The diagnosis was made bacteriologically, and the results of treatment were determined in the same way.

REPORT OF A CASE

S. R., a 21 year old white man who worked in a nutrition laboratory, was admitted to the Mount Sinai Hospital on April 17, 1946 and gave the following history: One week before his admission his temperature rose to 103 F. He experienced severe throbbing frontal headaches and chilly sensations. These symptoms persisted for two days. He then became afebrile, and fleeting pains in the knees and elbows developed. There was no tenderness or swelling of these joints. On the fourth day prior to his admission mild sore throat developed. On the third day before his entrance into the hospital a blotchy, flat, reddish, non-pruritic rash appeared on both arms and hands; this disappeared twenty-four hours later. Two days before he was admitted there were intermittent stabbing pains in the flanks and back.

On admission physical examination revealed that the patient was well developed, well nourished and moderately acutely ill. He complained of severe backache which was aggravated by motion. There was no tenderness in the costovertebral angle. The pharynx was slightly injected. Small, soft, nontender nodes were palpable in the axillary, inguinal and epitrochlear regions. The heart was of normal size, with a blowing systolic murmur over the apex. The liver and spleen were not palpable. The blood pressure was 114 systolic and 60 diastolic. The erythrocyte sedimentation rate was 2 mm. in one hour. The white blood cell count was 9,700, the differential count being normal. The hemoglobin content was 90 per cent, the temperature 100.2 F. and the pulse rate 100. The urine was normal. The Wassermann test elicited a negative reaction.

On the third day after his admission to the hospital the patient's temperature rose to 103.4 F., but neither the arthralgia nor the rash recurred. A blood culture incubated for seventy-two hours at a temperature of 37 C. revealed *Str. moniliformis*. By the sixth day after admission the temperature had fallen to normal and the patient was symptom free. He remained afebrile and asymptomatic thereafter until his discharge five weeks later.

After the organism had been identified, further questioning revealed that for three weeks prior to his admission the patient had worked as a helper in a commercial nutrition laboratory, in which he had cared for white laboratory rats. Two weeks before admission and one week prior to the onset of symptoms he was nipped on the right middle finger by one of the rats, severely enough to draw blood. There was no local inflammatory reaction, and the patient soon forgot the incident.

5. Wheeler, W. E.: Treatment of the Rat Bite Fevers with Penicillin, *Am. J. Dis. Child.* **69**:215 (April) 1945. Porter, J. E., and Foster, T. A.: Rat-Bite Fever, *J. Maine M. A.* **37**:93 (April) 1946. Watkins, C. G.: Ratbite Fever, *J. Pediat.* **28**:429 (April) 1946.

6. Heilman, F. R., and Herrell, W. E.: Penicillin in the Treatment of Experimental Infections with *Spirillum Minus* and *Streptobacillus Moniliformis* (Rat Bite Fever), *Proc. Staff Meet., Mayo Clin.* **19**:257 (May 17) 1944.

A second blood culture, taken four days after the first, was sterile. Third and fourth cultures, taken five and ten days later respectively, when the patient was still afebrile and asymptomatic, again yielded *Str. moniliformis*.

The micro-organism was found susceptible to 0.2 Oxford units of penicillin per cubic centimeter, or ten times the amount for the standard H strain of *Staphylococcus aureus*. The susceptibility to streptomycin was 1.0 unit per cubic centimeter, or five times the amount for the standard SM strain of *Staph. aureus*. Because of the persistent bacteremia, despite an afebrile and asymptomatic course, penicillin therapy was instituted. The patient received 100,000 units intramuscularly every three hours day and night for nineteen days. A blood level of 4 units per cubic centimeter of serum was obtained thirty minutes after an injection of the drug. Two blood cultures made during treatment and two weekly cultures made after cessation of treatment were all sterile. The patient was discharged six weeks after admission, apparently cured.

BACTERIOLOGY

Cultivation of Str. Moniliformis.—Blood cultures were of primary diagnostic importance in this case. The routine method for cultivation of blood currently employed in the department of bacteriology of this hospital was used. Twenty-three cubic centimeters of blood is drawn under sterile precautions and divided as follows: Five cubic centimeters is added to each of the following: veal infusion broth enriched with 1 per cent yeast extract; veal infusion broth with 2 per cent dextrose, and veal infusion broth with p-aminobenzoic acid (concentration, 0.001 per cent). Three pour plates are made by adding 2 cc. of blood to each of two tubes containing dextrose agar and one tube with plain agar, pouring the mixture into sterile Petri dishes and allowing it to harden. The last 2 cc. of blood is added to a tube containing veal infusion broth in which there is a slice of liver, and the tube is sealed with petrolatum for anaerobiosis. These are all incubated at a temperature of 37 C. Twenty-four hours later transplants are made from each of the flasks to tubes containing 1 per cent dextrose broth and into tubes containing liver and sealed with petrolatum. This procedure is repeated daily with samples from each flask and tube examined microscopically, until the culture becomes positive, or for two weeks if it remains sterile.

In the yeast and veal infusion and the 2 per cent dextrose and veal infusion the growth exhibited the typical "cotton ball" appearance at the bottom of the flasks. In the 1 per cent dextrose broth and in the tubes containing liver for anaerobiosis a granular growth adhered to the side of the containers. Spreads revealed the presence of extremely pleomorphic gram-negative organisms. There were some spiral and curved forms, but the most common variety was a long, slender filament with swelling at the end and at various points along the organism. These knobs were frequently gram-positive.

The organism, after being identified as *Str. moniliformis*, was inoculated on blood plates, on 20 per cent serum agar plates and in 20 per cent

serum broth tubes. Cultures incubated at a temperature of 37 C. aerobically, anaerobically under nitrogen and under 5 per cent carbon dioxide tension all showed good growth in twenty-four hours. In the tubes there was typical granular growth adherent to the sides. The plates revealed small, moist, glassy, round, discrete colonies measuring about 0.5 mm. in diameter. There was no hemolysis on human blood plates.

Spreads of twenty-four hour old cultures invariably showed the forms previously described. Spreads of forty-eight hour old cultures stained with Giemsa and Gram stains revealed less knobbing with a greater tendency to segmentation of the filament (i. e., the morphologic feature

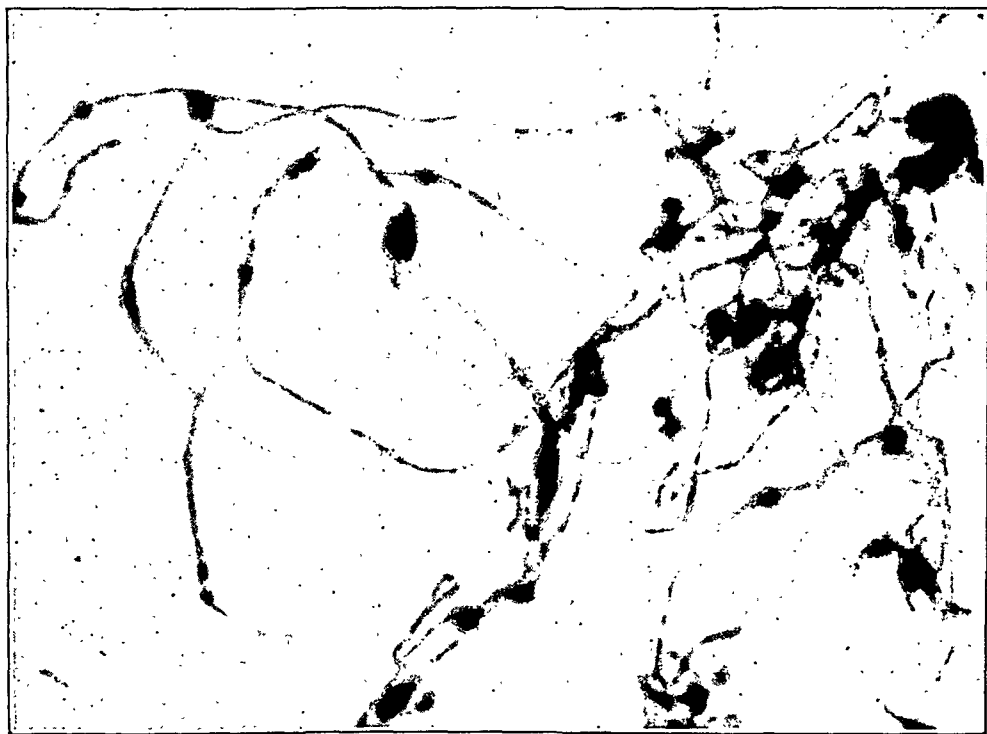


Fig. 1.—Twenty-four hour old culture of *Str. moniliformis* (2,500 \times). Note the knobbing and segmentation of the organism.

from which the name streptobacillus originated). The Gram stain also revealed a variability in the intensity of staining from light pink to red.

Examination of a twenty-four hour old culture under the electron microscope showed that knobbing was produced by bulging of a large amount of dense material. Comparative studies with the electron microscope on other micro-organisms suggest that the bulging material may be nuclear in nature.⁷ The segmented forms seem to consist of smaller amounts of the dense (nuclear?) material, with clear cytoplasm between each segment and a continuous cellular membrane.

7. Shwartzman, G.: Personal communication to the authors.

Agglutination Tests.—Agglutination tests were done in order to establish further the identity of the organism isolated in this case. For these tests the Parker serum (sent to Dr. Gregory Schwartzman by Dr. Frederick Parker Jr. some months ago) was used. The titer against *Str. moniliformis* given by Dr. Parker was 1:1,280. This serum completely agglutinated the strain isolated in this laboratory in a dilution of 1:880. A precipitin test with the use of Parker's serum and the supernatant fluid from a seventy-two hour old culture of 20 per cent serum broth gave a negative reaction.

An agglutination test made with a saline suspension of the organism and the patient's serum obtained on the fourteenth day in hospital gave

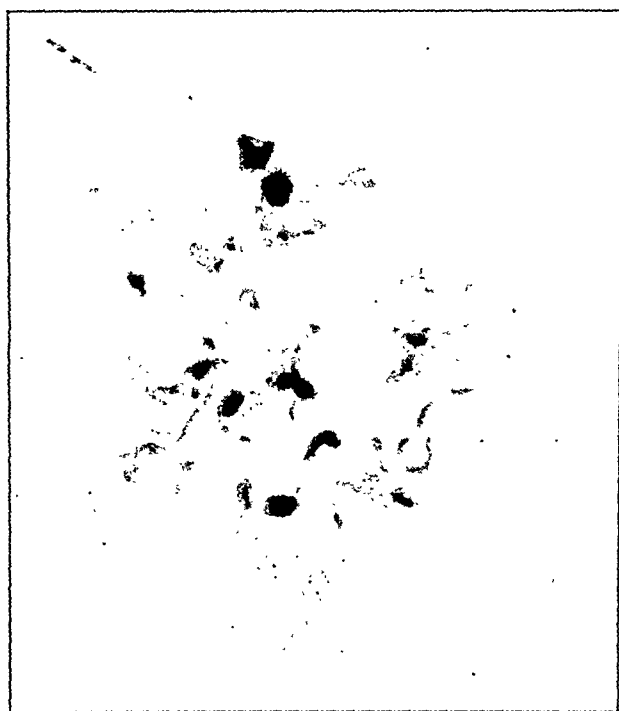


Fig. 2.—Seventy-two hour old culture of *Str. moniliformis* (2,500 \times). The organism is shorter than those in the younger culture, but knobbing and segmentation are still present.

a positive reaction in a dilution of 1:1,024. The results of subsequent agglutination tests were inconclusive because of the pronounced self agglutination of the suspension. Because of this difficulty, a smooth antigen was prepared by treating a twenty-four hour old growth with solution of formaldehyde. This was done by adding 0.15 cc. of 4 per cent solution of formaldehyde to 7.5 cc. of a twenty-four hour old serum broth culture and incubating at a temperature of 37 C. for three days. A saline suspension of the organism was then prepared and solution of formaldehyde added again in a final concentration of 2.6 per cent. The various dilutions of serum were mixed with 0.25 cc. of undiluted antigen and incubated in a water bath at a temperature of 37 C. With this

technic, the agglutination test gave a positive reaction in serum dilution of 1:600.

Inoculation of Animals.—Because of the rather mild clinical course, an attempt was made to study the pathogenicity of the strain of *Str. moniliformis* by inoculation of mice.

Swiss Mice.—Series I: Six mice received intraperitoneally 0.5 cc. of a saline suspension of the organism from a twenty-four hour old culture. Three were inoculated in the heel pad with 0.1 cc. of the suspension. One of the 6 animals inoculated intraperitoneally died in twenty-four hours. Cultures both of the heart's blood and of peritoneal scrapings yielded *Str. moniliformis*. A second mouse died eleven days after inoculation. A culture of the heart's blood revealed the streptobacillus. Peritoneal scrapings showed no organisms on direct spread or culture. The third mouse remained alive and well. It was killed after three

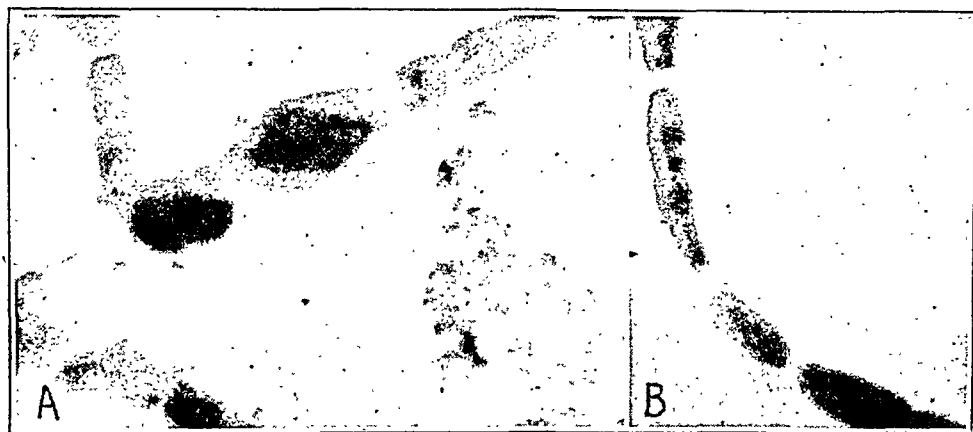


Fig. 3.—Photographs of *Str. moniliformis* taken with the electron microscope (A, 9,400 \times ; B, 7,500 \times) by Dr. Gregory Schwartzman. Note accumulation and bulging of dense (nuclear?) material to form knobs and segmentation. The continuous cell membrane and clear cytoplasm between segments are also evident.

weeks. Direct spreads and cultures of both the heart's blood and peritoneal scrapings were sterile. The remaining 3 mice inoculated intraperitoneally were killed after two, four and six days in order to rule out the presence of latent bacteremia. Cultures of peritoneal scrapings and the heart's blood were sterile in all 3.

Within six days the 3 mice inoculated in the heel pad showed swelling, stiffness, redness and heat in the ankle and knee joints on the side of the injection. All 3 mice died, 1 in eight days, 1 in eleven days and 1 in twelve days after inoculation. Microscopically, the affected joints showed partial destruction of the articular cartilage, with periostitis and perichondritis. The periarticular tissues showed acute and subacute inflammation and foci of necrosis. Necrotic tissue and inflammatory cells were present in the joint space. A Gram stain of the tissue revealed streptobacilli. Heart's blood of the first 2 that died yielded *Str. moniliformis* on culture. Direct spread and cultures of the blood from the third animal were sterile.

Series II: In these tests on Swiss mice mucin was combined with a saline suspension of the organism in order to increase the invasiveness of the latter.⁸ The mucin was prepared according to the method of Rake⁹ and others⁸ as follows: Fifteen grams of mucin was added to 3,000 cc. of distilled water and mixed for twenty minutes in an electric mixer. The resulting suspension was autoclaved at 15 pounds of pressure for fifteen minutes. Five grams of dextrose was added to 10 cc. of distilled water and sterilized at 12 pounds of pressure for twenty minutes. Six cubic centimeters of the solution of dextrose was added to the mucin mixture. The p_H was adjusted to 7.2 with dibasic sodium phosphate.

Three mice were inoculated intraperitoneally with 1 cc. of a saline suspension of the organisms and 1 cc. of mucin. All 3 animals died within forty-eight hours.

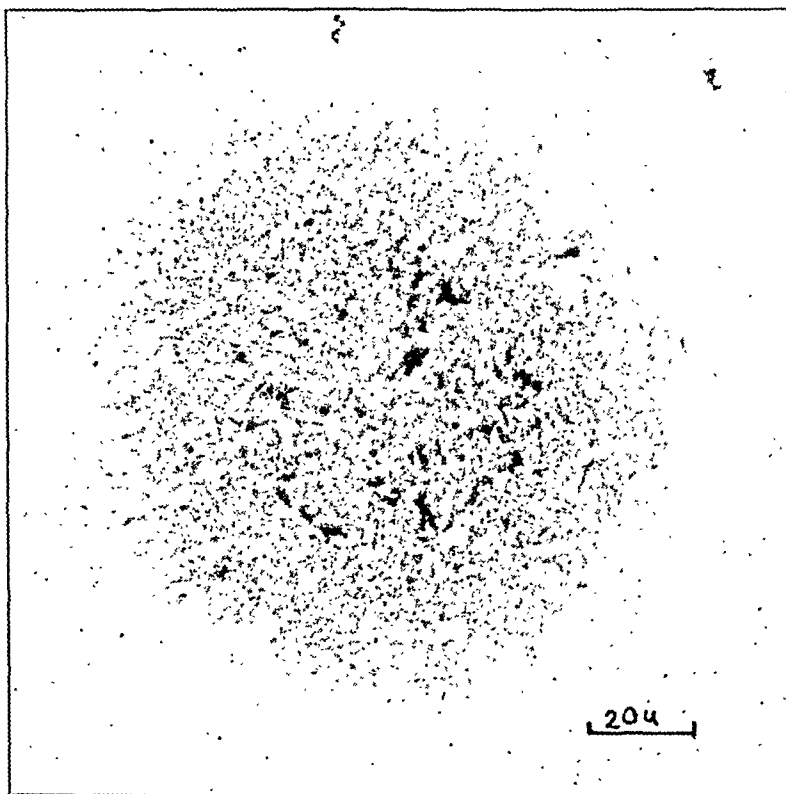


Fig. 4.— L_1 pleuropneumonia-like colony (500 \times). Note foamy periphery with characteristic wavy filaments, the "zooglia" of Brown and Nunemaker.^{1a}

Culture of the heart blood revealed *Str. moniliformis* in all the mice. Peritoneal scrapings from 2 animals also contained the organism. A fourth mouse, serving as control, received intraperitoneally 1 cc. of mucin and 1 cc. of isotonic solution of sodium chloride. It remained alive and well.

8. Miller, C. P.: Experimental Meningococcal Infection in Mice, *Science* 78:340 (Oct. 13) 1933. Miller, C. P., and Castles, R.: Experimental Meningococcal Infection in Mouse, *J. Infect. Dis.* 58:263 (May-June) 1936. Cohen, S. M.: A Study of the Virulence of Meningococcus Strains of the Protective Activity of Antimeningococcus Sera, *J. Immunol.* 30:203 (Feb.) 1936.

9. Rake, G.: Enhancement of Pathogenicity of Human Typhoid Organisms by Mucin, *Proc. Soc. Exper. Biol. & Med.* 32:1523 (June) 1935.

These observations indicate the low pathogenicity of the strain of streptobacillus recovered.

The Pleuropneumonia-like (L₁) Form.—In order to obtain the L₁ forms of Klieneberger¹⁰ usually found in association with the streptobacillus, blocks were cut out of ninety-six hour old cultures of the streptobacillus on blood agar plates. These blocks were inverted and pressed into fresh human blood agar plates. This procedure removes the loosely adherent surface colonies of the streptobacillus. Colonies of L₁ forms were then implanted by sliding the remnants of the block across the blood plates.

The L₁ colonies were minute and adherent to the agar. Transplants were made onto 20 per cent serum agar plates. When growth appeared, blocks were cut out, placed on slides and stained with Wayson's¹¹ stain. Microscopically, the colony had a darkly stained center with a foamy periphery. Inspection by means of oil immersion revealed the edges to be made of numerous wavy filaments, the "zooglia" of Brown and Nunemaker.¹²

SUMMARY AND CONCLUSIONS

A case of rat bite fever caused by *Streptobacillus moniliformis* is described. Initially, the clinical picture was typical, with a history of a rat bite followed one week later by fever, fleeting arthralgia, a rash and no local inflammatory reaction to the bite. This picture, however, was only transitory, and cultures of the blood continued to reveal the organism after the fever and other symptoms disappeared.

In vitro, the streptobacillus proved to be susceptible to penicillin and streptomycin. In vivo, penicillin was equally effective and promptly sterilized the blood stream.

The method of taking blood cultures was described and discussed.

Agglutination tests were performed to prove the identity of the organism and to determine the antibody titer in the serum of the patient.

Although the number of experiments was small, inoculation of animals suggested variation in the pathogenicity of the streptobacillus.

The L₁ form of Klieneberger was isolated.

Miss Beatrice Toharsky assisted in this work.

10. Klieneberger, E.: The Natural Occurrence of Pleuropneumonia-like Organism in Apparent Symbiosis with *Streptobacillus Moniliformis* and Other Bacteria, *J. Path. & Bact.* 40:93 (Jan.) 1935.

11. Meyer, K. F.: *The Newer Knowledge of Bacteriology and Immunology*, Chicago, University of Chicago Press, 1928.

EFFECT OF IRRADIATION, IMMUNITY AND OTHER FACTORS ON VACCINIAL INFECTION

A Review Illustrated by the Report of a Secondary Ocular Infection Treated
with Roentgen Rays

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THE PREVENTION of permanent impairment of vision is the goal in the treatment of any infection of the eye. Accidental ocular infection with vaccinia occurs usually as a complication of prophylactic immunization against smallpox. The eye may be inoculated by a transference of virus from the site of vaccination or from another's lesion or dressing. Rarely does infection occur as a laboratory accident in the course of the preparation or experimental use of the virus. The danger of ocular infection lies in involvement of the cornea, with subsequent development of an opaque scar.

Although millions of vaccinations are done yearly, the total number of cases of ocular infection with vaccinia reported to date only slightly exceeds 200.¹ Fortunately, the patient is usually partially immune at the time of inoculation of the eye. Infection of the lid and conjunctiva is relatively commoner than that of the cornea, and recovery is usually complete, with little residual scarring. Of 100 cases of ocular vaccinia reviewed in 1930, 27 involved the cornea and 12 resulted in the reduction of vision.²

Therapy is not standardized. The beneficial results obtained from the use of roentgen therapy in an accidental ocular infection in a par-

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1. Atkinson, W. S.; and Scullard, G.: Vaccinia with Ocular Involvement, *Arch. Ophth.* 23:584 (March) 1940.

2. Toulant, P.: Les complications oculaires de la vaccine, *Paris méd.* 2: 190 (Sept.) 1930.

tially immune human being suggested that irradiation might be a useful adjunct to other methods of treatment.

REPORT OF A CASE

A healthy 20 year old medical student was inoculated on the upper part of the left arm with smallpox vaccine by a combination of the multiple scratch and puncture technics. Ten small papules which appeared on the third day at the



Ocular vaccinia of five days' duration, secondary to primary inoculation in the arm ten days previously. The insert is a close view of the lesions on the lid, taken the following day, before roentgen therapy was instituted.

primary site of inoculation became vesicles by the fifth day. By the tenth day, one large umbilicated yellow pustule was present.

On the fifth day following inoculation of the arm three small, discrete, non-painful but itching papules appeared along the margin of the right lower eyelid. On the tenth day swelling and redness of the eye rapidly developed, until the eye was partially closed by edema.

The patient recalled no contamination at the time of inoculation or subsequently. He had never had smallpox, cowpox or chickenpox, and a single previous attempt at vaccination for smallpox nine years previously had not been successful.

When the patient was admitted to the hospital on the tenth day, the temperature was 102.6 F., and he appeared acutely ill. The entire right side of the face was red and edematous. Along the margin of the lower eyelid there were three umbilicated, yellow, encrusted vesicles, each 3 mm. in diameter. The conjunctiva was red; no involvement of the cornea was seen. The pustule on the lateral aspect of the left arm was surrounded by diffuse mild erythema and was less edematous than the eye. The accompanying photograph illustrates both lesions.

Cold boric acid compresses were applied, and packs of 20 per cent mild silver protein were placed between the lids. Two grams of sulfathiazole was given in a single dose. On the morning after the patient's admission to the hospital, the swelling and redness had increased and contact lesions were present along the margin of the upper lid. Roentgen therapy was given to the right eye on the morning of the second, third and fourth days in the hospital, 22 r per minute being given for four minutes on the first day and for three minutes each succeeding day. A total of 220 r in air was given at 120 kilovolts and 5 milliamperes, with a 2 mm. aluminum filter, at a distance of 30 cm. over a field of 10 by 10 cm. The half value layer equaled 3.60 mm. of aluminum.

The swelling and redness began to subside rapidly on the second day of roentgen therapy. Two days after the final treatment the lesion on the eye had almost disappeared. The patient was discharged on the eighth day in the hospital, (eighteenth postvaccinal day) with an encrusted lesion on the arm, slight edema and redness of the right eye and no impairment of vision. Recovery of the eye was complete.

Although acute vaccinal blepharoconjunctivitis characteristically subsides rapidly, improvement did not begin in this case until the initiation of roentgen therapy. A series of experiments on rabbits were undertaken in an effort to determine the value of this addition to the treatment and the optimum time for roentgen therapy in such cases; they are being reported separately.³

COMMENT

Vaccinal infection occurs when active virus meets a susceptible cell and becomes established intracellularly. Infection may be prevented or treated by measures designed (1) to inactivate the virus, (2) to alter the host cell and (3) to hinder the spread of the virus through tissue. The mechanism by which roentgen therapy may act is not clearly known.

The Value of Roentgen Therapy.—The experiments being reported elsewhere indicate that roentgen therapy for primary or secondary vaccinal infection of the eye diminishes the residual corneal opacities and hastens regression of the acute lesions. The optimum time for

3. Harrell, G. T.; Reid, C. H.; Little, J. M.; Mankin, J. W.; Pittman, H. W.; Holt, L. B., and Morris, L. M.: The Effect of Roentgen Therapy on Experimental Ocular Vaccinia in Non-Immune and Partially Immune Rabbits, to be published.

therapy would appear to be between the appearance of the lesion and the time it reaches its height. Treatment given early, as soon as inoculation is suspected, delays the appearance but does not prevent the full development of the lesion. If combined with local instillations of immune serum—which will be discussed further in following paragraphs—this delay in the development of a primary lesion might prevent disabling infection. The delay is probably not due to a direct action of roentgen rays on the virus. Experiments in vitro have shown that roentgen irradiation will reduce the infectivity of vaccinia lymph, but the dosage required is extremely high and would not be tolerated by the eye.⁴ Under the conditions of the experiments, roentgen therapy was not harmful to the eye.

Experimental evidence indicates that roentgen as well as other forms of irradiation is effective in the reduction of the extent of vaccinia lesions in the skin of rabbits.⁵ It is possible that radiation therapy acts by diminishing the rate of spread of the virus through tissue.

It is not proposed that irradiation should supplant other forms of therapy for ocular vaccinia but that it be used as an adjunct. Comparison of the effectiveness of roentgen therapy used alone and roentgen therapy combined with other types of treatment is difficult, because so few cases have been recorded in detail in the literature and so many combinations of therapy have been used.

The Role of Partial Immunity.—Immunity is an important factor in the prevention of disabling loss of vision following vaccinia infections, regardless of the form of therapy used. The ocular vaccinia infections observed in human beings usually are secondary to inoculation of the skin; hence secondary ocular infections are of greatest importance clinically. The secondary lesions of the cornea observed in experimental animals were less severe and resulted in less opacity than the primary corneal lesions whether roentgen therapy of the eye was used or not. We attribute this finding to the partial immunity of the cornea, which should have developed in the interim.

The Use of Serum: Immunity to vaccinia has been shown to be humoral as well as fixed tissue in type. It would therefore seem logical to instil immune serum locally in the conjunctival sac immediately after contamination and early in the course of the infection, in order to inactivate the virus before it has parasitized the cells of the eye. Convalescent

4. Gowen, J. W., and Lucas, A. M.: Reaction of Variola Vaccine Virus to Roentgen Rays, *Science* **90**:621 (Dec. 29) 1939.

5. (a) Le Fèvre de Arric, M.: Action empêchante des rayons X sur la vaccine expérimentale de lapin, *Compt. rend. Soc. de biol.* **96**:208 (Jan. 28) 1927.

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human serum has been found to be a potent antiserum.⁶ The parenteral administration of convalescent or hyperimmune serum to increase general humoral immunity after the infection is established has not been efficacious, though it is useful in other viral infections, such as measles. Parenterally administered immune serum will prevent vaccinia infection when given prophylactically to animals before inoculation; this measure has little practical application in ocular infections, however.⁷

The Use of Secondary Inoculation: The less severe lesions observed in animals which received secondary inoculation of the skin after the appearance of signs of primary infection in the eye suggest the value of this procedure in cases in which contamination of the human eye is suspected. General systemic immunity apparently develops slowly or incompletely after inoculation of immunizing antigens into the eye, while immunity has been shown to develop quickly after inoculation of the skin with vaccinia virus.⁸ It is possible that best results would be obtained by giving roentgen therapy and secondary vaccination of the skin simultaneously, soon after inoculation of the eye, but this variation was not tried experimentally. The use of secondary inoculation with vaccinia virus would be comparable in some respects to the prophylactic inoculation of patients thought to be infected with rabies virus. In that case immunity which develops as a result of systemic inoculation prevents the infection from becoming established in a portion of the body—the central nervous system—which itself participates poorly in immunity. Of course, the period of incubation is much shorter in vaccinia than it is in rabies.

Other Modes of Therapy.—*Attack on the Virus:* Ultraviolet rays and supersonic vibrations have been used in an attempt to inactivate the vaccinia virus or alter its virulence.⁹ Ultraviolet irradiation has less penetrating power than roentgen rays and would theoretically be less effective in tissue infection. Methods which are effective in vitro might not be tolerated by living tissues and hence may not be applicable to the treatment of patients. The optimum temperature for growth of

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8. Blattner, R. J.; Heys, F. M., and Gollub, S. W.: Antibody-Response to Cutaneous Inoculation with Vaccinia Virus in Human Subjects, Utilizing the Egg-Protection Technic: I. Serum-Virus Neutralization; II. Protection by Passive Transfer, *J. Immunol.* **46**:207 (April) 1943. Footnote 2.

9. Rivers, T. M., and Gates, F. L.: Ultra-Violet Light and Vaccine Virus: II. The Effect of Monochromatic Ultra-Violet Light upon Vaccine Virus, *J. Exper. Med.* **47**:45 (Jan.) 1928. Rivers, T. M.; Smedel, J. E., and Chambers, L. A.: Effect of Intense Sonic Vibrations on Elementary Bodies of Vaccinia, *J. Exper. Med.* **65**:677 (May) 1937.

the vaccinia virus in tissue culture has been shown to be 34 to 35 C. (93.2 to 95 F.); therefore, application by any means of as much local heat as the eye can tolerate would be indicated, regardless of other types of therapy.¹⁰

Since the vaccinia virus is an obligate intracellular parasite, any chemotherapeutic agent to be most effective would have to attack the virus before cells have become parasitized. Many such agents do not pass across cell membranes readily. Systemic administration of sulfonamide compounds have proved useless in the treatment of accidental or experimental vaccinia infections.¹¹ Penicillin given systemically has been shown to be ineffective against viruses except those of large size; the vaccinia virus is moderately large, but experiments in animals have shown no beneficial effect from the use of penicillin.¹² In vitro studies of local antiseptics have shown them to have little virucidal power except in concentrations too great for use in vivo.¹³ Alteration in vitro of the hydrogen ion concentration has been shown to inactivate the virus; a slight increase is more effective than a comparable decrease.¹⁴ The use of weak acids for irrigation or compresses would be indicated early but probably would be useless after the infection is established. Oxidizing agents have also been tested in vitro, but in concentrations which can be used clinically the agents must be locally applied for periods of an hour or more.¹⁵ Relatively small amounts of ascorbic acid, which probably acts as an oxidizing agent, have been shown to inactivate in vitro many times the infective dose of the vaccinia virus.¹⁶

Alteration of the Cell: Since viruses do not reproduce in the absence of living tissue, they are probably dependent on parasitized cells for factors essential to nutrition and respiration. It has been shown that rabbits in a poor state of nutrition are more resistant to virus infections

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11. Kolmer, J. A., and Brown, H.: Failure of Sulfanilamide in Treatment of Experimental Vaccinia Rabbits, *Proc. Soc. Exper. Biol. & Med.* **48**:138 (Oct.) 1941.

12. Andrews, C. H.; King, H., and van den Ende, M.: Chemotherapeutic Experiments with the Viruses of Influenza A, Lympho-Granuloma Venereum and Vaccinia, *J. Path. & Bact.* **55**:173 (April) 1943.

13. Dunham, W. B., and MacNeal, W. J.: Inactivation of Vaccinia Virus by Mild Antiseptics, *J. Lab. & Clin. Med.* **28**:947 (May) 1943.

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than are rabbits in a good state of nutrition.¹⁷ On the other hand, the systemic administration of ascorbic acid, methionine, choline and, to a less extent, betaine—the last three of which contain the biologically labile methyl group—inhibits dermal infection with vaccinia in the rabbit.¹⁸ It would therefore seem advisable to administer vitamin C and a natural source of the whole vitamin B complex, which would contain the aforementioned substances. The effect of immunity on the entrance of virus into cells is discussed previously.

Irradiation several days before inoculation with the virus has been reported to decrease the severity of dermal vaccinia.^{5a} On the other hand, damage of tissue from any physical agent immediately previous to inoculation may increase the extent of the lesion. In the absence of trauma the cornea appears to be naturally more resistant to vaccinia than other parts of the eye. Any mechanical procedure or drug which might cause even the most minute damage should be avoided.

Prevention of Spread Through Tissue.—Complete hydration of interstitial spaces apparently inhibits the spread of the virus.¹⁹ Since alterations in the intake of fluids have little effect on intracellular fluid, fluids should be forced. It has also been shown that the administration of estrogens will inhibit the spread of dermal vaccinia in rabbits.²⁰ The value of estrogenic therapy in ocular infection in human beings or in animals has not been determined. It is possible that roentgen therapy in the dosages employed may be effective in the localization of the virus and the delay of its entrance into the cells.

SUMMARY

An accidental human ocular infection with vaccinia virus, secondary to inoculation of the arm, was treated with roentgen therapy, without the development of residual scarring.

Partial immunity produced by inoculation of the skin helps to protect the cornea from permanent damage by vaccinial infection.

Other methods of therapy may help to inactivate the virus, alter its virulence, increase the resistance of the host cell or inhibit the spread of virus through tissue.

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18. Sprunt, D. H.: Inhibiting Effect of Methionine, Choline and Betaine on Rabbit's Susceptibility to Infection with Vaccinia, *Proc. Soc. Exper. Biol. & Med.* **51**:226 (Nov.) 1942.

19. Taylor, H. M., and Sprunt, D. H.: Increased Resistance to Viral Infection as a Result of Increased Fluid in Tissues, *J. Exper. Med.* **78**:91 (Aug.) 1943.

20. Sprunt, D. H.: The Effect of the Female Sex Hormones on Infection and Inflammations, *South. M. J.* **34**:288 (March) 1941.

EFFECT OF AMINO ACIDS ON THE FUNCTION OF THE MUSCLES OF PATIENTS WITH MYASTHENIA GRAVIS

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AND

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ACCORDING to a recently presented concept,¹ much of the symptomatology in patients with myasthenia gravis can be explained by a decreased acetylcholine synthesis. Amino acids² and proteins³ were found to increase the acetylcholine synthesis in vitro. It seemed reasonable, therefore, to investigate the effect of the infusion of amino acids on patients with myasthenia gravis.

METHOD

Records of muscle action potential were taken from healthy subjects and from patients with myasthenia gravis by the following method: The forearm was firmly fixed in the supine position onto a padded board by means of broad strips placed across the arm near the elbow and the wrist. Of the two silver recording electrodes (0.5 sq. cm.), one was fixed with adhesive tape to the skin over the ventral surface of the first phalanx of the fifth finger and the other over the surface of the hypothenar eminence at a distance of about 5 cm. from the first electrode. The electrodes were connected to the grid input terminals of a differential amplifier feeding into an oscilloscope. A ground electrode was placed on the forearm. The stimulating electrodes consisted of two metal plates, the larger being affixed to the skin over the triceps muscle and the smaller, a movable electrode 0.5 cm. in diameter, being pressed firmly against the skin over the ulnar nerve just above the elbow. Good contact was established by the use of electrode jelly over the skin, which was partially deprived of its epidermis by superficial scratching. Ten stimuli, each of one hundred microseconds' duration and of "supramaximal intensity," were used. The sweep circuit of the oscilloscope was synchronized with the stimulator so that successive stimuli and muscle action potentials were superimposed on the screen of the cathode ray tube. Ten con-

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From the New York Hospital and the Department of Medicine (Neurology) and Psychiatry, Cornell University Medical College.

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2. Torda, C., and Wolff, H. G.: *Proc. Soc. Exper. Biol. & Med.* **59**:181, 1945.

3. Torda, C., and Wolff, H. G.: *Federation Proc.* **5**:106, 1946.

secutive stimuli at a frequency of ten per second and the accompanying muscle action potentials were superimposed and photographically recorded from the screen of the cathode ray tube.

Measurements of muscle action potential were made for ten days every second day in the afternoon two hours after the administration of 22.5 mg. of neostigmine bromide. Afterward amino acids were given intravenously on six consecutive days in the form of amigen.⁴ One liter of a 5 per cent amigen solution containing 5 per cent dextrose was infused into the patient. Action potential records were taken one hour after the end of infusion of the amino acids.

MATERIAL

The effect of amino acids was studied in 5 patients with myasthenia gravis. The results obtained from 1 patient are presented in detail.

Patient G., a 42 year old woman, had had myasthenia gravis for seven years. In May 1946 she could not walk or stand and had pronounced ptosis of the left eyelid, and her extraocular movements were limited in all directions. She had profound weakness of the palate, tongue and muscles of deglutition. She could not raise her head from the pillow or her arms from the bed a distance of 20 cm. She could pat the bed with her hands only five or six times. She could not rise from a lying to a sitting position and was able to turn over in bed only with maximum effort. She could not raise her legs in a kicklike motion off the bed. She received 180 mg. of neostigmine bromide a day distributed over the waking hours and taken at two hour intervals. In these circumstances she was able to leave her bed for an armchair for her meals (total time not exceeding two hours daily). When neostigmine bromide was withheld longer than two hours she experienced extreme weakness, manifesting itself by the inability to swallow (even water) and by difficulty in breathing. Therefore, during the control period it was necessary to record the muscle action potentials of this patient two hours after administration of neostigmine bromide.

RESULTS

A short series of action potential records from healthy subjects is contained in figure 1. These records show that in healthy subjects the amplitude of the muscle action potential is maintained during electrical stimulation of the motor nerve at a frequency of ten pulses per second.

Figure 2 represents a series of action potential records of patient G taken during the control period. The first stimulus applied to the

4. Amigen is a pancreatic digest of casein containing amino acids and polypeptides (Mead Johnson and Company). The calculated content of the essential amino acids in amigen are: methionine, 3 per cent; arginine, 5.5 per cent; histidine, 2 per cent; lysine, 5.8 per cent; tryptophane, 1 per cent; phenylalanine, 5.6 per cent; threonine, 4.5 per cent; valine, 5 per cent; leucine, 13.5 per cent, and isoleucine, 4.8 per cent. Chemical analysis of amigen shows the composition to be as follows: total nitrogen, 12 per cent; potential amino nitrogen, 10.5 per cent, and actual amino nitrogen, 7.8 per cent. The approximate mineral composition of amigen is as follows: sodium, 1.5 per cent; phosphorus, 0.9 per cent; sulfur, 0.6 per cent; calcium, 0.1 per cent; potassium, 0.3 per cent; magnesium, 0.05 per cent; iron, 0.02 per cent, and copper, 0.002 per cent.

ulnar nerve was followed by the largest action potential, and a drop in the amplitude of the action potential was observed during continuation of the stimulation of the ulnar nerve. There was a considerable daily variation in the drop in the amplitude of the muscle action potential occurring between the first and the maintained amplitude. Figure 2 *A* shows slightly more than a 50 per cent drop and figure 2 *B* nearly a 100 per cent drop; figure 2 *C*, taken half an hour after administration of 22.5 mg. of neostigmine bromide following the record in figure 2 *B*, shows less than a 90 per cent decrease of the amplitude of the action potential; figure 2 *D* shows approximately a 55 per cent decrease, and figure 2 *E* nearly an 83 per cent decrease.

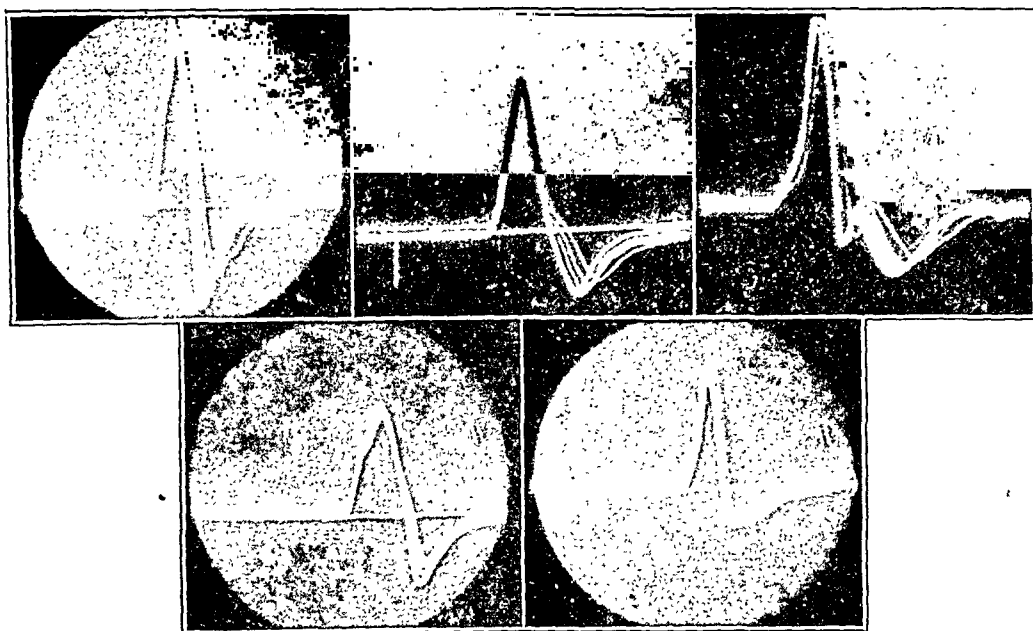


Fig. 1.—Records of the muscle action potential of 5 healthy subjects.

Figure 3 shows records taken one hour after infusion of amino acids on the third, fifth and sixth days of infusion. On the third and fifth days records of muscle action potential were taken three hours after the administration of the usual amount of neostigmine bromide (i. e., 22.5 mg.) and on the sixth day four and a half hours after the administration of neostigmine bromide. (Because of the amino acids, the patient was able to postpone the taking of neostigmine bromide.) These records show a maintenance of the amplitude of the action potential at the same level during the stimulation of the motor nerve. They resemble the records of muscle action potential of healthy subjects (fig. 1). The patient stated that she felt stronger, and she walked without help.

Measurements of muscle action potential of 4 less severely ill patients with myasthenia gravis were taken under the conditions just described. The patients showed a less pronounced decrease in the amplitude of muscle action potential during the control period. The infusion of amino acids in these patients resulted in an improvement in muscle function, manifesting itself in an increased performance of work and decreased daily requirements of neostigmine bromide during the period of administration of amino acids.

COMMENT

The foregoing results suggest that infusion of amino acids may augment the muscle action potential and improve the function of the

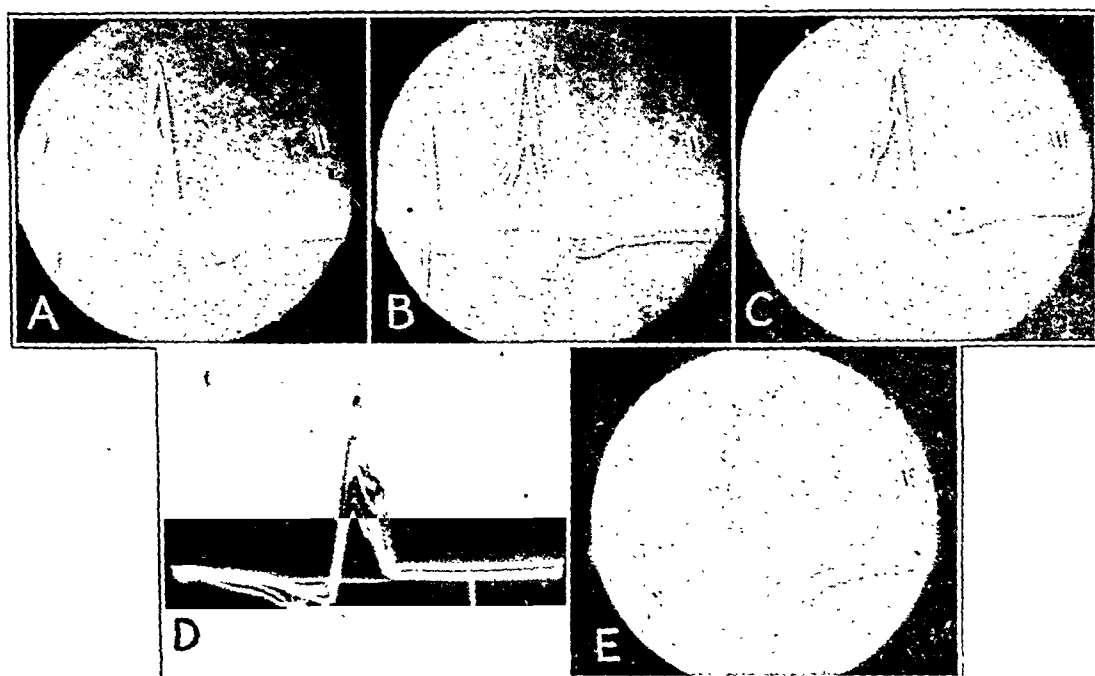


Fig. 2.—Records of the muscle action potential of patient G with myasthenia gravis (control period). *A*, third day after admission to the hospital and two hours after administration of neostigmine bromide; *B*, fifth day after admission, two hours after administration of neostigmine bromide; *C*, fifth day after admission, half an hour after administration of neostigmine bromide (half an hour after *B* was taken); *D*, seventh day after admission, two hours after administration of neostigmine bromide; *E*, ninth day after admission, two hours after administration of neostigmine bromide.

muscles in patients with myasthenia gravis. General inferences may not be drawn from these results because of our inability to find a greater number of patients suitable for these particular electromyographic studies.

The mechanism of action of amino acids on muscle function in the aforementioned experiments is not yet established. Perhaps it is justifiable to point out that the described effect of the amino acids on the action potential may implicate several entirely different processes,

e. g., (1) supplying an essential amino acid to muscle or nerve, (2) augmenting some not yet identified enzymatic process and (3) increasing acetylcholine synthesis in a specific or nonspecific way. The last concept seems to us the most attractive for the following reasons: (a) It has been demonstrated that in patients with myasthenia gravis,¹ there is a defect in acetylcholine synthesis. (b) Amino acids were found to increase acetylcholine synthesis in vitro.² (c) The known decline of the amplitude of muscle action potential during prolonged stimulation of the motor nerve in patients with myasthenia gravis may be temporarily prevented by the administration of acetylcholine and neostigmine

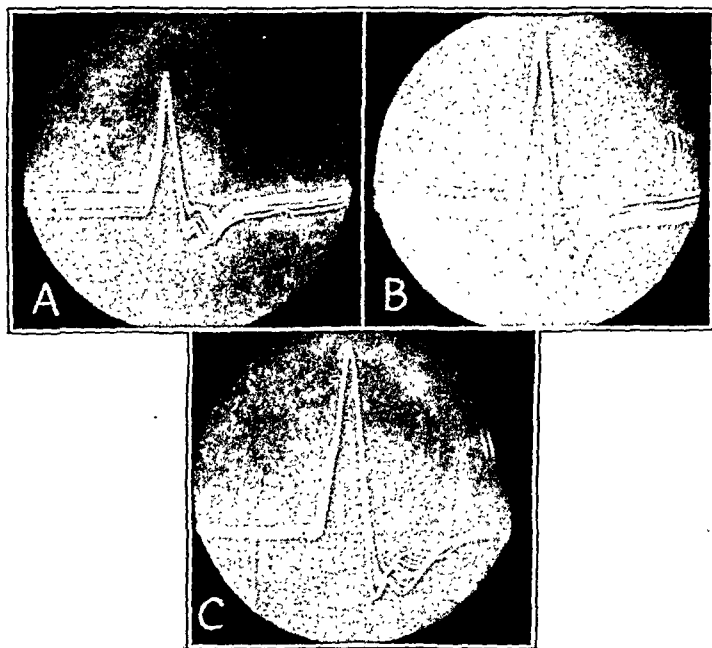


Fig. 3.—Records of muscle action potential of patient G with myasthenia gravis after administration of amino acids. *A*, records taken after the third daily infusion of amino acids, three hours after neostigmine bromide was administered; *B*, records taken after the fifth daily infusion of amino acids, three hours after neostigmine bromide was administered. *C*, records taken after the sixth daily infusion of amino acids, four and a half hours after neostigmine bromide was administered.

bromide.⁵ (d) An improvement in muscle function and muscle action potential followed the infusion of amino acids in the experiments presented here. It is, therefore, possible that the improvement in muscle action potential noted is referable to increased acetylcholine synthesis due to the administration of amino acids.

No therapeutic implications are justifiable from these preliminary experiments.

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TORDA-WOLFF—MYASTHENIA GRAVIS

SUMMARY

The effect of infusion of amino acids on patients with myasthenia gravis was studied. The known decline of the amplitude of muscle action potential following prolonged indirect stimulation was prevented by infusion of amino acids.

Dr. Charles Berry, Department of Anatomy, Cornell University Medical College, took all records with the differential amplifier and associated equipment of his design and construction.

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INCREASED CATABOLISM FOLLOWING ACUTE MYOCARDIAL INFARCTION

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IT IS well known that a disturbance of carbohydrate metabolism characterized by hyperglycemia and, at times, glycosuria may occur after myocardial infarction. Less generally recognized is the appearance of creatinuria in patients with the latter disorder.¹ These phenomena suggest the occurrence of changes in metabolism after myocardial infarction which resemble those described in other conditions of stress or damage, such as trauma,² burns,³ exposure to cold⁴ and infection.⁵

From the Medical Service and Medical Research Laboratories, Beth Israel Hospital, and the Department of Medicine, Harvard Medical School.

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(Footnotes continued on next page)

Indeed, a recent study by Davidson and others^{5b} records the occurrence of striking changes in intermediary metabolism in a patient in shock after myocardial infarction. The last-named authors^{5b} stressed the role of shock as the factor responsible for the changes observed, but in view of the fact that similar changes have been described in patients not in shock with infection or after trauma,⁶ it seemed important to study patients with myocardial infarction who were not in a state of collapse.

MATERIAL AND METHODS

Three men, respectively 44, 59 and 52 years old, were studied. The diagnosis of myocardial infarction was made in each instance on the basis of the history of typical crushing precordial pain lasting several hours, associated with weakness and sweating and followed by the development of moderate fever for a few days, leukocytosis, accelerated sedimentation of the red blood cells and characteristic changes in the electrocardiogram. None had a history of diabetes or of overt renal disease; 1 of them (case 2) had had two similar episodes, the last eleven months previously. After the subsidence of the pain, pronounced sweating did not occur and dyspnea and hypotension were not found. Observations were begun within a few hours after the admission of the patients to the hospital. They ingested a balanced diet containing 65 to 100 Gm. of protein and 1,400 to 2,100 calories per day. It was necessary to encourage them to maintain their intake of food at this level during the period of study. Two other men, aged 42 and 58 years respectively, were kept in bed for ten days as control subjects; the diagnoses were mild exertional angina pectoris in 1 and psychoneurosis with mild hypertrophic arthritis in the other.

The intake of nitrogen was calculated from the weighed food intake, on the basis of the tables of Bridges and Mattice.⁷ The nitrogen output was measured by analyzing all urine and feces by the Kjeldahl method. Measurements of various chemical components of the blood were made with the patient in the fasting state. The methods used were as follows: for blood sugar, that of Folin⁸; for lactate, that of Barker and Summerson⁹; for pyruvate, that of Bueding and Wortis¹⁰;

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for blood amino nitrogen, that of Danielson¹¹; for nonprotein nitrogen, that of Folin and Wu¹²; for total plasma protein, a modified micro-Kjeldahl steam distillation method; for urinary protein, the method of Alexander and Derow,¹³ and for creatine and creatinine, the method of Folin and Dennis.¹⁴

OBSERVATIONS

Each of the 3 patients exhibited a negative nitrogen balance during the first five days of the study, the loss averaging between 4.4 and 8.1 Gm. per day; the loss of nitrogen during the next five days diminished in all, and during the third five days the nitrogen metabolism approached

TABLE 1.—*Intake and Output of Nitrogen*

Case	First Five Days			Second Five Days			Third Five Days		
	Intake, Gm.	Output, Gm.	Average Loss, Gm./Day	Intake, Gm.	Output, Gm.	Average Loss, Gm./Day	Intake, Gm.	Output, Gm.	Average Loss, Gm./Day
1.....	53.7	80.1	5.3	72.3	88.7	3.3	77.9	87.0	1.8
2.....	50.4	90.8	8.1	77.2	106.1	5.8	80.9	115.9	7.0
3.....	52.3	74.5	4.4	62.4	75.4	2.6	64.2	68.6	0.9

TABLE 2.—*Output of Urinary Albumin*

Case	Duration, Days	Daily Excretion, Mg.	Total Excretion, Mg.
1.....	3	95 to 225	488
2.....	3	99 to 186	387
3.....	3	55 to 160	299

TABLE 3.—*Output of Urinary Creatine*

Case	Duration, Days	Daily Excretion, Mg.	Average Excretion, Mg.
1.....	12	19 to 199	74
2.....	12	11 to 239	66
3.....	5	14 to 39	32

balance in 2 of the subjects (table 1). The 2 control subjects showed little net loss of nitrogen, the total loss for the ten day period of study being 3.8 and 5.8 Gm. respectively. The albuminuria found in the first

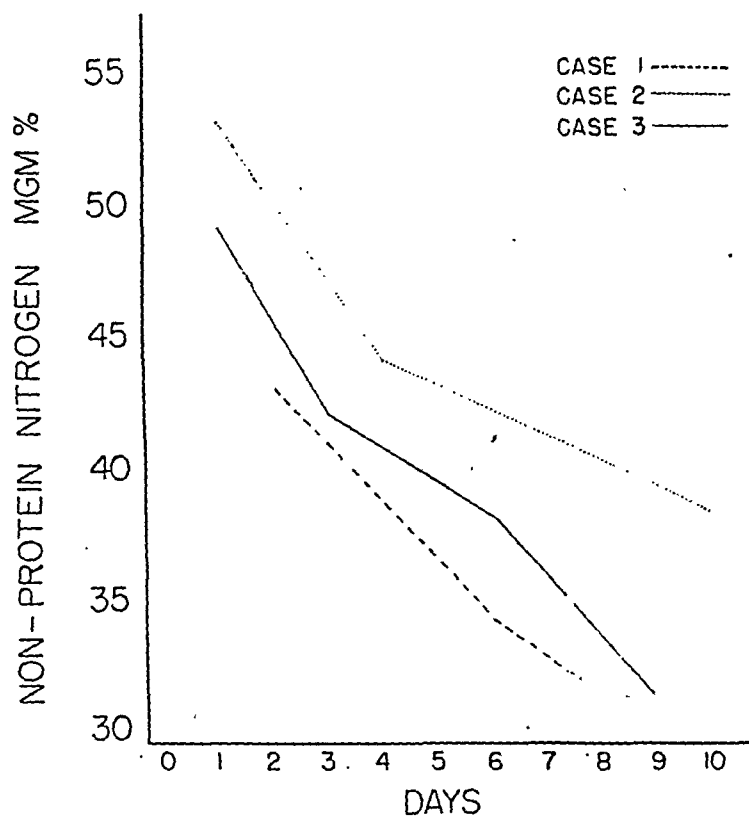
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three days in each of the patients studied was small in amount; the daily output of albumin did not exceed 225 mg. and totaled only 299 to 488 mg. for the entire period (table 2). The plasma protein levels showed no significant changes during the period of study. The blood nonprotein nitrogen levels were somewhat increased early in the course, reaching levels of 43 to 53 mg. per hundred cubic centimeters; they soon fell to normal, however (chart). Creatinuria, absent in the 2 control subjects, occurred in all 3 of the patients with myocardial infarction and lasted from five to twelve days (table 3), diminishing toward the end of that period. Creatine was detected in the first specimen of urine passed by the



Changes in the blood nonprotein nitrogen level.

TABLE 4.—*Carbohydrate Metabolism in Patients Studied*

Case	Blood Sugar, Mg. %		Blood Pyruvate, Mg. %		Blood Lactate, Mg. %		Blood Amino Nitrogen, Mg. %	
	Initial	Final	Initial	Final	Initial	Final	Initial	Final
1.....	97	93	1.5	1.0	17.7	11.7	9.0	5.9
2.....	92	88	1.9	1.1	16.4	12.1	8.5	5.2
3.....	128	90	1.0	0.8	14.3	11.2	6.6	5.6

patients after entering the hospital. The blood amino nitrogen levels were elevated to 6.6 to 9.0 mg. per hundred cubic centimeters initially, but they fell to normal at the end of the study.

A few studies of carbohydrate metabolism revealed no significant change in blood sugar concentration in the patients studied and only small increases in blood lactate and pyruvate levels (table 4).

COMMENT

The data of the present study show the existence of a preponderance of catabolic activity following myocardial infarction even in the absence of prolonged shock. The daily loss of nitrogen, which averaged 4.4 to 8.1 Gm. per day in the patients studied, is to be contrasted with an average daily loss of 0.38 to 0.58 Gm. per day in the control subjects; the latter figures are within the range found by Cuthbertson¹⁵ in normal subjects kept in bed. Similarly, the creatinuria observed in the present study, in corroboration of the earlier findings of Herrmann and Decherd,¹ is also evidence of a metabolic disturbance, for it was detectable in the first specimen of urine obtained here and could not have been a consequence of prolonged rest in bed or of the fever which developed later. It is worthy of note that unpublished data obtained for 1 patient with myocardial infarction who manifested shock and pulmonary edema for a week after admission to the hospital showed a negative nitrogen balance and creatinuria over twice as great as that in the patients without shock here presented. The rise in blood nonprotein nitrogen level which occurs not infrequently following myocardial infarction is probably the result of increased delivery of nitrogen to the kidneys consequent to increased protein catabolism at a time when renal function may be decreased as a consequence of vasoconstriction or, in some cases, of shock. The elevation of blood amino nitrogen level found in the patients studied here was probably also a consequence of increased destruction of body protein.

The slight increases in blood lactate and pyruvate levels which occurred in the patients of the present study are probably another indication of increased catabolism; the patients were chosen for this investigation because they showed no evidence of peripheral vascular stasis or pulmonary edema which might have given rise to tissue anoxia. It is to be expected, however, that in patients in whom tissue anoxia develops after myocardial infarction the increases in blood lactate and pyruvate concentration would be greater than those found here; indeed, a few unpublished data support this supposition.

The importance of fever in the causation of the metabolic changes observed after myocardial infarction, as after burns or trauma, is difficult to evaluate. In the present study the fever lasted only a few days and did not reach high levels. Nevertheless, in those patients in whom the febrile response is definite and prolonged, the fever itself, by accelerating

15. Cuthbertson, D. P.: The Influence of Prolonged Muscular Rest on Metabolism, *Biochem. J.* **23**:1328, 1929.

catabolism, would make the changes in the nitrogen balance and in the chemical findings in the blood more pronounced.

The cause of the development of a preponderance of catabolic activity after myocardial infarction has not been studied; in other conditions of stress or damage, abnormal function of the adrenal cortex has been implicated.¹⁶ As in other conditions of damage, the period following myocardial infarction may be characterized by depression and persistent weakness and occasionally also by anorexia and wasting. It appears, therefore, that the metabolic and also the clinical characteristics of myocardial infarction, including hyperglycemia and elevated blood non-protein nitrogen level, resemble those of the "alarm reaction." It is to be noted that the changes found in the present study occurred in the absence of evidences of persistent collapse.

The data of the present study may possibly have some bearing also on the problem of the cause of the icterus following myocardial infarction. The explanation usually advanced for this phenomenon is that hepatic damage occurs as a consequence of acute congestion of the liver due to the cardiac lesion; indeed, some clinicians go so far as to consider icterus in myocardial infarction as evidence of localization of the area of necrosis in the right ventricle. Clinical experience, however, shows that detectable hepatic engorgement is not uncommonly absent in patients in whom icterus develops after cardiac infarction. It is of interest that unexplained hyperbilirubinemia is known to occur in patients with severe thyrotoxicosis or thermal burns, in persons subjected to excessively high and prolonged artificial fevers¹⁷ and in men after a marathon run.¹⁸ All these conditions are also characterized by a negative nitrogen balance, hyperglycemia and elevation of the blood lactate and pyruvate levels. It appears to be reasonable to add myocardial infarction to the list of conditions in which decided and prolonged catabolic activity may

16. Weil, P. G., and Browne, J. S. L.: The Excretion of Cortin Under Condition of Damage, *J. Clin. Investigation* **19**:772, 1940. Selye, H., and Dosne, C.: Influence of Traumatic Shock on Blood Sugar of Adrenalectomized Rats Treated with Adrenal Cortical Extract, *Proc. Soc. Exper. Biol. & Med.* **48**:532, 1941; Physiological Significance of Compensatory Adrenal Atrophy, *Endocrinology* **30**: 581, 1942. Albert, S.: Changes in Adrenal Function During the Alarm Reaction, *Proc. Soc. Exper. Biol. & Med.* **51**:212, 1942. Albright, F.: Cushing's Syndrome, in *Harvey Lectures*, Lancaster, Pa., Science Press Printing Company, 1943, vol. 38, p. 123. Selye, H.: The General Adaptation Syndrome and the Diseases of Adaptation, *J. Clin. Endocrinol.* **6**:117, 1946.

17. Keutmann, E. H.; Bassett, S. H., and Warren, S. L.: Electrolyte Balances During Artificial Fever with Special Reference to Loss Through the Skin, *J. Clin. Investigation* **18**:239, 1939. Wallace, J., and Bushby, S. R. M.: Physiological and Biochemical Changes Following Hypertherm Treatment, *Brit. J. Ven. Dis.* **19**:155, 1943.

18. Gilligan, D. R.; Altschule, M. D., and Katersky, E. M.: Physiological Intravascular Hemolysis of Exercise: Hemoglobinemia and Hemoglobinuria Following Cross-Country Runs, *J. Clin. Investigation* **22**:859, 1943.

be followed by hyperbilirubinemia. The precise cause of the apparent depression of hepatic function in all these conditions is not known, although it is of interest that the metabolic changes in conditions of stress or damage are effected through the liver.¹⁹

CONCLUSIONS

Three patients with myocardial infarction in whom persistent shock did not occur showed creatinuria, negative nitrogen balance and increase of blood nonprotein nitrogen concentration. Blood lactate, pyruvate and amino acid levels were also elevated slightly. These findings are similar to those reported by other authors in a variety of conditions of damage to the organism.

Miss Dorothy Youland and Miss Esther Issenberg, of the Dietary Department, assisted in this study.

330 Brookline Avenue, Boston.

19. Selye, H., and Dosne, C.: Effect of Cortin After Partial and After Complete Hepatectomy, *Am. J. Physiol.* **128**:729, 1940.

BASAL METABOLIC RATE IN HYPERTENSIVE VASCULAR DISEASE

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IN RECENT years great strides have been made in the direction of determination of the pathogenesis of hypertensive vascular disease. However, there is conflicting opinion concerning the relation between basal heat production and hypertensive vascular disease.¹ Clinically, an elevated basal metabolic rate has been noted in patients with hypertension. Mountain and his co-workers^{1b} reported that there was a direct correlation between basal heat production and the height of the blood pressure; others² failed to demonstrate this relation.

The exact mechanism underlying these metabolic changes has not been definitely proved. Some investigators³ have indicated that an

From the Department of Medicine and the Respiration Laboratory, New York Post-Graduate Medical School and Hospital.

1. (a) Boothby, W. M., and Sandiford, I.: Summary of the Basal Metabolism Data on 8,614 Subjects with Especial Reference to the Normal Standards for the Estimation of the Basal Metabolic Rate, *J. Biol. Chem.* **54**:783, 1922. (b) DuBois, E. F.: *Basal Metabolism in Health and Disease*, ed. 3, Philadelphia, Lea & Febiger, 1936, p. 325. (c) Boothby, W. M., and Willius, F. A.: Basal Metabolic Rate in Cases of Primary Cardiac Disease, *M. Clin. North America* **8**:1171, 1925. (d) Shapiro, S.: The Basal Metabolic Rate in Cases of Chronic Cardiac Disease and in Cases of Hypertension, *Arch. Int. Med.* **38**:385 (Sept.) 1926. (e) Aub, J. C., and DuBois, E. F.: The Respiratory Metabolism in Nephritis, *Arch. Int. Med.* **19**:865 (May, pt. 2) 1917. (f) Hayasaka, E.: On the Basal Metabolism in Hypertension, *Tohoku J. Exper. Med.* **12**:270, 1929. (g) Reznitskaya, E. Y., and Spivak, R. Y.: Basal Metabolism in Hypertonia, *Klin. med.* **16**:1410, 1938. (h) Mountain, G. E.; Allen, E. V., and Haines, S. F.: The Basal Metabolic Rate in Essential Hypertension, *Am. Heart J.* **26**:528, 1943. (i) Weiss, S., and Ellis, L. B.: The Quantitative Aspects and Dynamics of the Circulatory Mechanism in Arterial Hypertension, *ibid.* **5**:448, 1930. (j) Becker, J.: Grundumsatz und Hypertonie, *Ztschr. f. klin. Med.* **119**:412, 1932. (k) Mosler, E., and Edelstein, M.: Hypertension: Grundumsatz und Arteriosklerose im Alter, *Ztschr. f. d. ges. phys. Therap.* **35**:172, 1928. (l) Crile, G., Jr., and McCullagh, E. P.: Hypertension Simulating Hyperthyroidism, *M. Clin. North America* **24**:395, 1940. (m) Hamilton, R. L., and Beck, W. C.: Hypertension Simulating Thyrotoxicosis, *M. J. & Rec.* **135**:571, 1932.

2. Casullo, C. A.: El metabolismo basal en la hipertension arterial, *Semana méd.* **50**:27, 1943. Reznitskaya and Spivak.^{1g}

(Footnotes continued on next page)

interrelationship among the brain, the thyroid and the adrenal sympathetic system exists. Hayasaka¹² concluded that the basal metabolic rate remains unchanged in hypertensive patients with normal renal function but becomes elevated in those with renal insufficiency.

Because of these opposing viewpoints, it seemed of real value to reinvestigate the entire problem. In the present study of patients with hypertensive vascular disease, an attempt is made to determine (1) the frequency distribution of the basal metabolic rate; (2) the relation between basal heat production and (a) components of blood pressure, (b) pulse pressure and (c) tension of carbon dioxide in expired air; (3) the possible effect of abnormalities of the heart and kidneys on metabolism, and (4) the influence of the sympathetic nervous system on basal metabolism.

Since basal heat production has been found to be below normal in Addison's disease, hypothyroidism, lipid nephrosis, obesity due to pituitary or hypothalamic disorders and starvation and above normal in cardiorenal disease with dyspnea, diabetes insipidus, fever, hyperthyroidism, leukemia and polycythemia,⁴ patients with hypertensive vascular disease were eliminated whenever these pathologic conditions were found to be present.

METHOD AND MATERIAL

For this investigation a total of 115 patients (36 men and 79 women) with hypertensive vascular disease were selected from the records of the departments of medicine and surgery and the Respiration Laboratory of the New York Post-Graduate Hospital.⁵ The period of observation was from January 1943 to September 1946.

The blood pressure of each patient was obtained by the auscultatory method, a mercurial sphygmomanometer being used. The degree of impairment of the heart was determined by checking the electrocardiographic, 6 foot (1.82 meters) silhouette and the physical condition. Renal function was evaluated after intravenous urographic studies, concentration tests by the Mosenthal method and with the use of betahypophenamine, urea clearance tests, routine urine analysis and quantitative estimation of the blood urea nitrogen, nonprotein nitrogen and creatinine contents.

3. (a) Crile, G. W.: The Interdependence of Thyroid, Adrenals and Nervous System, *Am. J. Surg.* 6:616, 1929; (b) The Mechanism of Exophthalmic Goiter, *Tr. Third Internat. Goiter Conf. & Am. A. Study Goiter*, 1938, p. 1. (c) Knight, R. T.: The Use of Spinal Anesthesia to Control Sympathetic Overactivity in Hyperthyroidism, *Anesthesiology* 6:225, 1945. (d) McCartney, J. L.: Anxiety Overstimulating the Thyroid Gland: Psychogenic Exophthalmic Goiter, *Tr. Third Internat. Goiter Conf. & Am. A. Study Goiter*, 1938, p. 49. (e) Maddock, W. G.; Collier, F. A., and Pedersen, S.: Thyroid Crisis: Its Relation to Liver Function and Adrenalin, *Tr. Am. A. Study Goiter*, 1936, p. 61. Weiss and Ellis.¹¹ Becker.¹³

4. Best, C. H., and Taylor, N. B.: *The Physiological Basis of Medical Practice*, ed. 4, Baltimore, Williams & Wilkins Company, 1945, p. 536.

5. Dr. Cameron V. Bailey, Director of the Respiration Laboratory, permitted us to use unpublished data, and Dr. J. William Hinton, Department of Surgery, made available to us records of hypertensive patients.

The basal metabolic rates were determined, in all but 18 patients, at the Respiration Laboratory of the New York Post-Graduate Hospital by the use of the gasometer. The Tissot, or open circuit, apparatus, in which the subject breathes atmospheric air, was employed. Expired air was collected in a 100 liter gasometer, from which duplicate samples were removed for analysis by the Haldane-Henderson technic.⁶ This method allows for the simultaneous estimation of the partial pressure of carbon dioxide in expired air, the respiratory quotient and the basal metabolic rate. Elsewhere, Bruger and Rosenkrantz,⁷ Boyer and Bailey⁸ and Bailey⁹ have described the actual procedures and various modifications of the apparatus. The remaining 18 patients were studied at Doctors' Hospital, New York, by the Benedict-Roth¹⁰ method. For each method, the normal value for the basal metabolic rate is from +10 per cent to -10 per cent.

Six patients with increased heat production were restudied to evaluate the effect of a two stage thoracolumbar sympathectomy.¹¹ Five patients returned nine months to twenty-five months and 1 patient one week after this procedure. The Smithwick¹² technic was employed in 2 patients and a modified method¹³ in 4 others. The latter approach includes the removal of ganglions from the second lumbar to the fourth or third thoracic nerves as well as the complete greater, lesser and least splanchnic nerves.

RESULTS

From chart 1 it is apparent that 30 of the hypertensive patients, or 26.1 per cent, had an elevated basal metabolic rate of over +10 per cent; 20 of these, or 17.4 per cent, had a basal metabolic rate of over +15 per cent. At the other end of the scale, 14 of the patients, or 12.2 per cent, were found to have a basal metabolic rate below -10 per cent.

6. (a) Haldane, J. S.: *Methods of Air Analysis*, London, C. Griffen & Co., 1912. (b) Henderson, Y.: *Haldane Gas Analyzer*, *J. Biol. Chem.* **33**:31, 1918.

7. Bruger, M., and Rosenkrantz, J. A.: *Arteriosclerosis and Hypothyroidism: Observations on Their Possible Interrelationship*, *J. Clin. Endocrinol.* **2**:176, 1942.

8. Boyer, P. K., and Bailey, C. V.: *Concentration of Carbon Dioxide in Expired Air*, *Arch. Int. Med.* **69**:773 (May) 1942.

9. (a) Bailey, C. V.: *Apparatus Used in the Estimation of Basal Metabolism*, *J. Lab. & Clin. Med.* **6**:657, 1921; (b) *Notes on Apparatus Used in Determining the Respiratory Exchange in Man: I. An Adaptation of the French Gas Mask for Use in Respiratory Work*, *J. Biol. Chem.* **47**:277, 1921; (c) *A Low Resistance Air Valve*, *Proc. Soc. Exper. Biol. & Med.* **24**:184, 1926. (d) Hawk, P. B., and Bergeim, O.: *Practical Physiological Chemistry*, ed. 9, Philadelphia, P. Blakiston's Son & Co., 1926, appendix.

10. (a) Benedict, F. G.: *Portable Respiration Apparatus for Clinical Use*, Boston M. & S. J. **178**:667, 1918. (b) Roth, P.: *Modifications of Apparatus and Improved Technic Adaptable to Benedict Type of Respiration Apparatus*, *ibid.* **186**:457, 1922.

11. Performed by Dr. J. William Hinton, Department of Surgery, New York Post-Graduate Hospital.

12. Smithwick, R. H.: *Experiences with Surgical Treatment of Hypertensive Cardiovascular Disease in Man*, *Cleveland Clin. Quart.* **12**:105, 1945.

13. Hinton, J. W., and Lord, J. W., Jr.: *Thoraco-Lumbar Sympathectomy in the Treatment of Advanced Essential Hypertension*, *New York State J. Med.* **46**:1223, 1946.

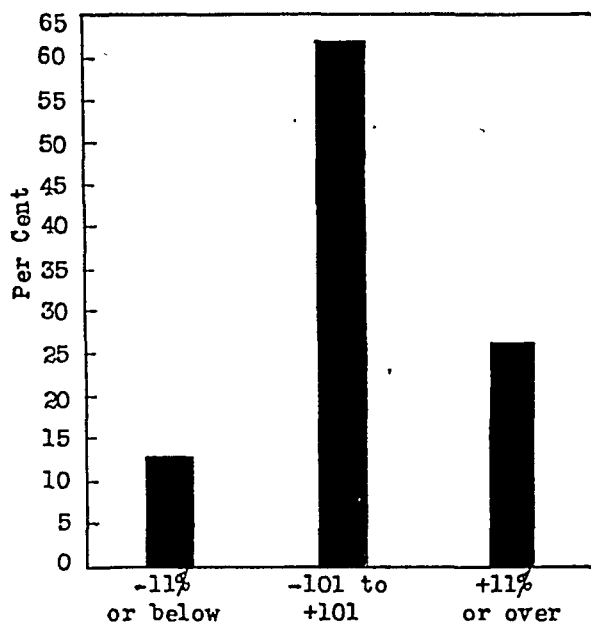


Chart 1.—Frequency distribution of the basal metabolic rate in 115 hypertensive patients.

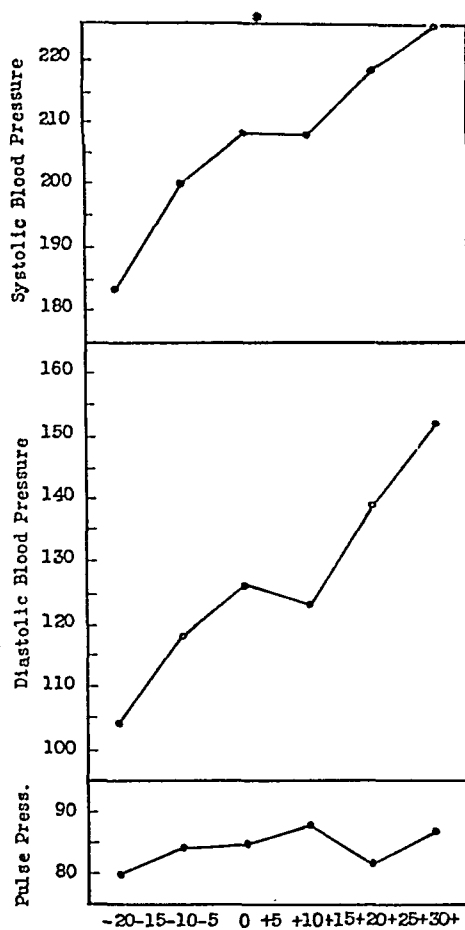


Chart 2.—The relation of the basal metabolic rate to the average systolic, diastolic and pulse pressure in 115 hypertensive patients.

Chart 2 demonstrates the relationship between the basal metabolic rate and the average systolic, diastolic and pulse pressure. In hypertensive patients in whom the basal metabolic rate was -20 per cent, the average systolic blood pressure was 183.5 mm. of mercury; with the metabolism at average normal the systolic blood pressure was 208.5 mm. of mercury, and when the basal heat production was $+30$ per cent or more the systolic blood pressure was 225.0 mm. of mercury. The levels of diastolic blood pressure were 104.3, 126.8 and 152.5 mm. of mercury at the basal metabolic rate of -20 per cent, average normal, and $+30$ per cent or more respectively. Similar plotted averages of pulse pressure demonstrated that at these basal metabolic rates the pressure was 80.0, 85.0 and 87.5 mm. of mercury respectively. There is, therefore, a decided positive correlation between basal metabolic rate and both systolic and diastolic blood pressure. On the other hand, there appears to be no significant association between basal heat production and pulse pressure.

TABLE 1.—*Incidence of Cardiac and Renal Dysfunction in One Hundred and Fifteen Patients with Hypertensive Vascular Disease as Related to the Basal Metabolic Rate*

	Total No.	With Cardiac Dysfunction		With Renal Dysfunction		With Both Car- diac and Renal Dysfunction	
		No.	%	No.	%	No.	%
Elevated basal metabolic rate.....	30	23	76.7	20	66.7	17	56.7
Normal and subnormal basal metabolic rate.....	85	55	64.7	29	34.1	23	27.1

An analysis of the partial pressure of carbon dioxide in expired air for each person with hypertension revealed that patients with a basal metabolic rate of $+11$ per cent or more had an average carbon dioxide tension of 19.81 as compared with 19.83 in those with a normal or subnormal metabolic rate.

The ages of hypertensive patients with elevated metabolic rates ranged from 29 to 60 years, with an average of 46.0 years; for those with normal or subnormal basal heat production the range was 23 to 74 years, with an average of 47.5 years.

Analysis of table 1 reveals that 76.7 per cent of hypertensive patients with elevated basal metabolic rates had some abnormality of the heart while 64.7 per cent of those in the normal or subnormal group had some cardiac derangement. On the other hand, the incidence of renal dysfunction or both cardiac and renal abnormalities in hypertensive patients with an elevated metabolic rate was 66.7 and 56.7 per cent respectively. This was undoubtedly a greater incidence than that found among those with the normal or subnormal metabolic rates in whom the proportions were 34.1 and 27.1 per cent respectively.

Table 2 summarizes the effect of thoracolumbar sympathectomy on the basal metabolic rate and blood pressure of 5 hypertensive patients

nine to twenty-five months following surgical intervention; 1 patient was reexamined one week following the same procedure. All patients showed a pronounced decrease in the average basal metabolic rate—from +27 to +9 per cent; in 4 patients it returned to normal levels. In contrast, the hypertensive levels of blood pressure were not affected by this procedure in 5 patients but returned to a normal of 110 systolic and 70 diastolic in the 1 patient who was restudied one week after operation.

TABLE 2.—*The Effect of Thoracolumbar Sympathectomy on the Basal Metabolic Rate and Blood Pressure of Six Hypertensive Patients*

Case	Age, Yr.	Basal Metabolic Rate, %	Blood Pressure	Interval After Operation
1.....	41	+16 + 4	228/124 204/130	25 mo.
2.....	45	+12 + 2	170/105 178/ 96	13 mo.
3.....	46	+16 + 6	210/120 210/120	10 mo.
4.....	53	+21 0	210/140 166/106	9 mo.
5.....	45	+39 +17	240/150 260/152	14 mo.
6.....	45	+55 +21	220/160 110/ 70	1 wk.

COMMENT

The incidence of hypermetabolism in this series of hypertensive patients agrees with that reported by DuBois and Boothby and Sandiford.^{1a,b} It has been maintained by others that hypertension and cardiac disease per se do not increase basal heat production unless cardiac decompensation and dyspnea are present.¹⁴ In this investigation patients with frank decompensation or dyspnea were excluded. Therefore, these findings may be regarded as representative of those in a group of hyper-

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tensive patients without cardiac insufficiency in whom elevated metabolic rates were noted.

Boyer and Bailey¹⁵ demonstrated that as the degree of decompensation increased the concentration of carbon dioxide in expired air decreased and as cardiac efficiency improved the carbon dioxide tension was restored to normal. In this study the average partial pressure of carbon dioxide in expired air was found to be normal for the entire group of hypertensive patients, regardless of associated elevated, normal or depressed metabolic rates. In all probability, in the absence of cardiac failure hypertension is necessary for some persons to maintain effective flow of blood through the brain and lungs.

Further analysis revealed that there is a greater incidence of renal dysfunction in hypertensive patients with increased basal metabolic rates than in those with normal or subnormal basal heat production. This, of course, might be due to the fact that those with renal dysfunction had a greater elevation in blood pressure. These results agree with the findings reported by Hayasaka.¹⁴ The direct correlation between the basal metabolic rate and both systolic and diastolic blood pressure is significant and is in agreement with the work of Mountain and his co-workers^{14b}; however, it fails to support the results of other investigators.²

Bruger and Rosenkrantz⁷ have shown that the basal metabolic rate decreases with advancing years in patients over 55 years of age but that the incidence of hypometabolism is greater for those exhibiting arteriosclerosis than for those without arteriosclerotic manifestations. In this study age and arteriosclerosis were not influencing factors, since the average age fell below 55 years and there was no significant difference in the average age of the hypertensive patients with elevated metabolic rates as compared with the age of those with normal or subnormal metabolic rates.

The possibility that thoracolumbar sympathectomy can lower basal metabolic rates may explain one of the mechanisms producing elevated metabolic rates in some hypertensive patients. It has also long been held that hyperadrenalism and an overactive sympathetic nervous system are associated with hyperthyroidism and elevated metabolic rates.³ Bruger, Rosenkrantz and Lowenstein¹⁶ presented some theoretic considerations suggesting that the fact that hypertensive patients have a low urinary excretion of 17-ketosteroids might reflect an exhausted adrenal gland caused by the constant strain of a persistent elevation in blood pressure. Spinal anesthesia to the fifth or fourth thoracic level,¹⁷ the removal of one adrenal or the denervation of the adrenal

15. Boyer, P. K., and Bailey, C. V.: Concentration of Carbon Dioxide in Expired Air in Heart Disease, *Arch. Int. Med.* **71**:529 (April) 1943.

16. Bruger, M.; Rosenkrantz, J. A., and Lowenstein, B. E.: Studies on the Morphology of the Adrenal Cortex and on the Excretion of 17-Ketosteroids in Hypertensive Patients, *Am. J. M. Sc.* **208**:212, 1944.

17. Peabody, Meyer and DuBois.^{14b} Hamburger and Lev.^{14c} Lev and Hamburger.^{14d}

glands ^{3a,b} has been shown to interrupt the lines of communication among the brain, the thyroid and the adrenal sympathetic system, thereby causing a reversal of the hyperthyroid state toward normal. Experimentally, the administration of ergotamine tartrate causes a fall in basal heat production in normal and thyroidectomized rabbits.¹⁸ Conversely, it has been reported that administration of epinephrine raises the basal metabolic rate.⁴ In hypertensive patients with elevated metabolic rates, Weiss and Ellis¹¹ performed thyroidectomies, while Becker¹¹ treated the thyroid with radiation; these procedures lowered the basal metabolic rate but had no effect on the level of preexisting arterial hypertension. In this investigation thoracolumbar sympathectomy likewise interrupted the interrelationship between the systems; there was a similar reduction of basal heat production without an appreciable alteration of the blood pressure. One must consider that cardiac work also may be a factor in elevating metabolic rate, since a direct correlation between basal metabolic rates and systolic and diastolic blood pressure as well as a greater incidence of renal dysfunction was found in this series of hypertensive patients with elevated metabolic rates.

SUMMARY

In hypertensive vascular disease without cardiac insufficiency a significant incidence of hypermetabolism has been demonstrated. The elevated metabolic rate may be due to the overactivity of the sympathetic nervous system through its interrelationship among the brain, the thyroid and adrenal-sympathetic system. Increased cardiac work may be an accessory factor in the increase of basal heat production. There was a direct correlation between the basal metabolic rate and the systolic and diastolic blood pressure; there was also a greater incidence of renal dysfunction or pathologic involvement of both kidney and heart in hypertensive patients with elevated metabolic rates. The partial pressure of carbon dioxide in expired air of hypertensive patients with normal cardiac function was found to be within normal limits. It is possible that hypertension is necessary in some persons to maintain adequate circulation through brain and lung, as manifested by the normal tension of carbon dioxide in expired air.

18. Marine, D.; Deutch, M., and Cipra, A.: Effect of Ergotamine Tartrate on the Heat Production of Normal and Thyroidectomized Rabbits, *Proc. Soc. Exper. Biol. & Med.* **24**:662, 1926.

Progress in Internal Medicine

GASTROENTEROLOGY

A Review of the Literature from July 1945 to July 1946

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(Concluded from Page 680)

SARCOMA

A malignant extramedullary plasma cell tumor arising in the stomach and metastasizing to the retroperitoneal space is described by Couret.¹⁷⁸ The exact nature of the process was not recognized until the histologic examination—although the clinical, roentgenologic and gross pathologic evidence indicated a malignant obstructive lesion of the pylorus. Histologically, the resemblance between plasma cell tumors and actively proliferating chronic inflammatory cells may make the differentiation troublesome.

A reticulum cell sarcoma is reported by Cash and Rappoport.¹⁷⁹

CARCINOMA

Carcinogenic Hydrocarbons.—Beck¹⁸⁰ studied the carcinogenic effect of hydrocarbons on the stomach of CBA mice. No tumors occurred in the glandular stomachs when 0.01 mg. of dibenzanthracene was given daily for three to ninety-seven weeks followed by a 0.1 per cent croton oil soap solution up to ninety weeks. However, in each of the 6 mice surviving for forty-two weeks in the group receiving benzpyrene tumors of the forestomach (two papillomas and four carcinomas) were found. Two papillomas were observed among 10 mice surviving seventy-two weeks in the group receiving dibenzanthracene.

178. Couret, J. S.: Extramedullary Plasma Cell Tumor of the Stomach: A Case Report, *Am. J. Clin. Path.* **16**:213-219, 1946.

179. Cash, I. I., and Rappoport, A. E.: Reticulum Cell Sarcoma of the Stomach, *Gastroenterology* **6**:40-49, 1946.

180. Beck, S.: The Effect of Feeding Carcinogenic Hydrocarbons Dissolved in Aqueous Soap Solution on the Stomach of CBA Mice, *Brit. J. Exper. Path.* **27**:155-157, 1946.

Dietary Factors.—In a comparison by Dunham and Brunschwig¹⁸¹ of the dietary and related factors acting during a fifteen to twenty year period before the onset of disease in 40 patients with and 40 without malignant gastric tumors, no significant differences were found.

Laboratory Studies.—Dunham and Brunschwig¹⁸² determined the calcium content of the gastric juice in 14 patients with gastric tumors and in 24 control patients. The differences could be explained on the basis of the higher acidity in the controls. Similar determinations of potassium in 9 patients with gastric tumors and in 11 controls disclosed no significant differences. The calcium and potassium contents were found to be increased in the secretions of 5 patients with achlorhydria induced by roentgenologic treatment of duodenal ulcer. Gastric tumors tissue contained relatively less calcium and more potassium than the adjacent uninvolved mucosa. In a benign papilloma with two separate carcinomas and also in a lymphosarcoma a similar potassium-calcium ratio was noted, suggesting that the abnormality is characteristic of neoplasm in general rather than of carcinoma alone.¹⁸³

Ficarra¹⁸⁴ has shown that in patients with gastric cancer the level of uric acid in the blood rises as the plasma protein level falls. The hyperuricemia results from accelerated endogenous protein metabolism and hence it helps in the evaluation of the hypoproteinemia already present. Further, it is of assistance in foretelling postoperative complication; the higher the blood uric acid level, the poorer the prognosis.

In a series of 140 patients with carcinoma of the stomach Colp¹⁸⁵ found values for free hydrochloric acid ranging from 20 to 60 millimols per liter in over one half; the combined acid values ranged from 40 to 113 millimols per liter. In 50 patients with no free acidity the combined acidity varied from 10 to 80 millimols per liter. Absolute achlorhydria was present in only 12. Alessandri and others,¹⁸⁶ in a series of 154 cases of gastric cancer, found achlorhydria in response to administration of histamine in 81.1 per cent, hypochlorhydria in 3.89 per cent, normo-

181. Dunham, L. J., and Brunschwig, A.: A Review of Dietary and Related Habits in Patients with Malignant Gastric Neoplasms, *Gastroenterology* **6**:286-293, 1946.

182. Dunham, L. J., and Brunschwig, A.: Calcium and Potassium Content of Secretions from Noncancerous and Cancerous Stomachs, *Cancer Research* **6**:54-56, 1946.

183. Brunschwig, A.; Dunham, L., and Nichols, S.: Potassium and Calcium Content of Gastric Carcinoma, *Cancer Research* **6**:230-232, 1946.

184. Ficarra, B. J.: Hyperuricemia in Gastric Cancer, *Surgery* **19**:223-228, 1946.

185. Colp, R., and Druckerman, L.: Subtotal and Palliative Gastrectomy for Chronic Gastric Ulcer, *Surgery* **18**:573-582, 1945.

186. Alessandri, R. H.; Lerner, J., and Sanz del Fierro, R.: El jugo gástrico en las lesiones gástricas malignas, *Rev. méd. de Chile* **73**:793-795, 1945.

chlorhydria in 9 per cent and hyperchlorhydria in 5.8 per cent. Lactic acid was found in the gastric secretion in 28.1 per cent and macroscopic blood in 24.3 per cent.

Barber and Franklin¹⁸⁷ took swabs for bacteriologic examinations directly from the mucosa of the stomach and duodenum during operations on 50 patients undergoing partial gastrectomy for peptic ulcer or gastric carcinoma. Bacteria were isolated from sixteen of forty benign ulcers and from nine of ten carcinomas. Micrococcus albicans, nonhemolytic streptococci and coliform bacilli were found in many instances despite a normal or high gastric acidity. Pyogenic cocci, i. e., Streptococcus pneumoniae, Staphylococcus aureus and Lancefield A hemolytic streptococci, were isolated in 7 cases.

Diagnosis.—In 500 men without digestive symptoms and over 45 years of age subjected to roentgenographic examination of the esophagus, stomach and duodenum, Dailey and Miller¹⁸⁸ found gastric carcinoma in none, antral gastritis in 1, suspected antral polyp in 1 and gastric ulcer in 1. Consequently, the authors conclude that routine roentgenograms of the gastroduodenal tract on symptomless persons are not worth while.

Several authors emphasize the difficulties in the clinical and roentgenologic diagnosis of early cancer. Alvarez¹⁸⁹ presents a case to illustrate the fact that a short history of gastric "ulcer" in persons past middle life usually indicates the presence of cancer; the results of gastric analysis are of little diagnostic value, and the disappearance of the crater with improvement under medical management should not lead to any relaxation of vigilance. Golob¹⁹⁰ reviews the mistakes made; Engel¹⁹¹ discusses the various aspects of the problem. The roentgenologic difficulties are reviewed by Savignac,¹⁹² Diaz and others¹⁹³ and Ledoux-Lebard and associates,¹⁹⁴ who emphasize the

187. Barber, M., and Franklin, R. H.: Bacteriology of Stomach and Duodenum in Cases of Peptic Ulcer and Gastric Carcinoma, Brit. M. J. **1**:951-953, 1946.

188. Dailey, M. E., and Miller, E. R.: A Search for Symptomless Gastric Cancer in Five Hundred Apparently Healthy Men of Forty-Five and Over, Gastroenterology **5**:1-4, 1945.

189. Alvarez, W. C.: Things to Do if Cancer of the Stomach Is Oftener to Be Cured, Gastroenterology **6**:574-575, 1946.

190. Golob, M.: Gastric Carcinoma: Review of Errors in Diagnosis, Am. J. Digest. Dis. **13**:17-22, 1946.

191. Engel, G. C.: Carcinoma of the Stomach and Its Problems, Clinics **4**:13-26, 1945.

192. Savignac, R.: Le diagnostic radiologique précoce du cancer de l'estomac; essai de synthèse, Arch. d. mal. de l'app. digestif **34**:167-180, 1945.

193. Diaz, F.; Donoso, A., and Velasco, F.: Diagnóstico radiológico de lesiones gástricas infiltrantes pequeñas y sospechosas de malignidad, Rev. méd. de Chile **73**:667-677, 1945.

fact that simple decrease in the size of the niche, with clinical improvement, must be interpreted with reservation because this change may occur with a malignant lesion. Tumen,¹⁹⁵ after a similar careful review of the differential features, concludes that if doubt as to the nature of the lesion still remains after a brief therapeutic trial it is much safer to proceed with operation than to wait for too long a time and thus deny the patient the possibility of successful surgical treatment.

Pathologic Features.—Rickles¹⁹⁶ reports an instance of four independent papillary adenocarcinomas apparently arising from adenomatous polypi and an ulcerating carcinoma of the cardiac end of the same stomach infiltrating the muscularis, with metastases to the perigastric lymph nodes. Heller¹⁹⁷ reports a primary carcinoma of the stomach, with multiple annular stenosing carcinomatous infiltrations of the small intestine and colon, resembling granulomatous inflammatory lesions. The author attributes this type of metastasis to blockage of the mediastinal lymphatic channels and retrograde dissemination of the tumor cells through the abdominal lymphatic vessels.

Surgical Treatment.—Koster and Trolle¹⁹⁸ have made an elaborate study of hemoconcentration, plasma proteins and blood electrolytes in postoperative shock after gastrectomy, which will be read with interest by those concerned with the subject but need not be reviewed here.

In a review of 208 cases of carcinoma of the stomach, Lawrence and Kay¹⁹⁹ found that 9 patients, constituting 18.7 per cent of those subjected to radical operations or 30 per cent of those surviving resection, lived five years. The great losses in carcinoma are due to inoperability, unresectability and postoperative mortality. Patients who survive gastrectomy have one chance in three of living five years.

Moutier²⁰⁰ reports a decreasing mortality in operations on the stomach. Moreland²⁰¹ reports 6 consecutive cases of gastrectomy

194. Ledoux-Lebard, R.; Ledoux-Lebard, G.; Crozat, J., and Pannetier, G.: Les niches géantes de l'estomac, *Arch. d. mal. de l'app. digestif* **34**:207-222, 1945.

195. Tumen, H. J.: An Evaluation of Criteria Useful in the Differentiation of Benign and Malignant Lesions of the Stomach, *Pennsylvania M. J.* **49**:609-614, 1946.

196. Rickles, J. A.: Multiple Carcinomas of the Stomach, *Surgery* **19**:229-236, 1946.

197. Heller, E. L.: Carcinoma of the Stomach with Multiple Annular Metastatic Intestinal Infiltrations, *Arch. Path.* **40**:392-398 (Nov.-Dec.) 1945.

198. Koster, K. H., and Trolle, D.: Investigations of Postoperative Shock: Haemoconcentration, Plasma Protein and Blood Electrolytes After Gastrectomy, *Acta chir. Scandinav.* **93**:51-80, 1946.

199. Lawrence, E. A., and Kay, J. H.: Carcinoma of the Stomach, *Surgery* **19**:504-514, 1946.

200. Moutier, F.: Gastrectomies et mortalité postopératoire, *Arch. d. mal. de l'app. digestif* **34**:164-167, 1945.

201. Moreland, R. B.: Total Gastrectomy, *Arch. Surg.* **52**:603-609 (May) 1946.

without fatality. The procedure is not incompatible with good health and gainful employment. Beaver, Gendel and Papper²⁰² record a total gastrectomy for linitis plastica with postoperative recovery.

Waugh and Fahlund,²⁰³ in reviewing 77 cases of total gastrectomy between 1920 and 1943 in which the patient was operated on, note a progressive increase in the frequency of the operation and a decrease in the mortality rate from an average of 60.6 per cent in the first twenty-two years to 25 per cent in 1943. More than half of the patients who survived total gastrectomy for cancer lived two or more years.

A perforated carcinoma of the stomach, complicated by sub-diaphragmatic abscess, was successfully resected twenty-two days after perforation by Jorboe and Pratt.²⁰⁴ The value of sulfonamide compounds and penicillin is stressed.

Radiation Therapy.—Fairchild and Shorter²⁰⁵ are studying the possibilities of direct irradiation combined with surgical treatments. In 9 cases of intra-abdominal cancer, 6 involving the stomach, 1 the abdominal esophagus, 1 the pancreas and 1 the descending colon, all considered bad risks for any operative procedure, 5 of the patients were reported to be doing well at over eighteen months, fifteen months, fifteen months, seven months, and five months respectively after therapy. It is pointed out that with increased experience the selection of cases will be improved and the technic of radiotherapy enhanced. The procedure is as follows: After thorough preoperative investigation and preparation, the abdomen is explored. At this point the surgeon, radiotherapist, pathologist and anesthetist jointly confer to decide whether the lesion is (1) operable, (2) inoperable but suited for curative direct irradiation, (3) suitable for palliative direct irradiation only, (4) suitable for palliative operation only or (5) unsuitable for any treatment. Further reports will be awaited with interest.

DUODENUM

Diverticula.—Centeno,²⁰⁶ in a series of 7,772 autopsies, found diverticula of the gastrointestinal tract in 64 instances, located as follows: esophagus, 12; stomach, 5; duodenum, 20; jejunum and ileum, 1; Meckel's, 12, and colon, 14. In 55 patients the diagnosis of diverticula

202. Beaver, M. G.; Gendel, S., and Papper, E. M.: Total Gastrectomy for Complete Carcinomatous Involvement of the Stomach, *Am. J. Surg.* **71**:813-821, 1946.

203. Waugh, J. M., and Fahlund, G. T. R.: Total Gastrectomy, *S. Clin. North America* **25**:903-917, 1945.

204. Jorboe, J. P., and Pratt, J. H.: Perforated Gastric Carcinoma Treated by Resection: Case Report, *Proc. Staff Meet., Mayo Clin.* **20**:446-448, 1945.

205. Fairchild, G. C., and Shorter, A.: Direct Irradiation of Cancer of the Stomach and Other Viscera, *Lancet* **2**:522-526, 1945.

206. Centeno, A. M.: Diverticulos del duodeno, *Rev. Asoc. méd. argent.* **59**:1397-1403, 1945.

of the duodenum was made by roentgenologic examination. In 36 the second portion was involved, in 9 the third portion and in 8 the fourth portion; 2 had double diverticula. In these 55 cases several other associated diseases were present, explaining the multiple symptoms.

Obstruction.—Kautz, Lisa and Kraft,²⁰⁷ in studying congenital duodenal obstruction, found that of 300 cases in the literature about 50 of the patients were operated on and half of these survived. Six cases are reported. Congenital duodenal obstruction is due to atresia. Complete atresia is twice as frequent as partial atresia. The clinical findings are those of high intestinal obstruction immediately after birth: dilatation of the stomach, distention of the duodenum, sometimes with an hourglass appearance, complete six hour residue and a lack of intestinal pattern.

Drucker and Cohen²⁰⁸ report an instance of a 23 year old woman with tremendous dilatation of the first and second portions of the duodenum. The dilatations ended abruptly in a constriction which resembled a cordlike rigid band a few millimeters in diameter. The diaphragm was incised successfully.

Price and Chang²⁰⁹ report an instance of a newborn infant with atresia of the small intestine who had in addition a subhepatic abscess and a large abscess of the liver, with calcific deposits in the fibrous wall.

In a discussion of acute gastroduodenal obstruction in adults, Beck²¹⁰ emphasizes the diagnostic importance of careful roentgenologic studies. The obstruction is usually caused by compression of the third portion of the duodenum between the superior mesenteric vessels and the abdominal aorta. It occurs in the debilitated patient who is forced to lie on his back and is aggravated by any condition producing a downward tension of the mesenteric vessels. The essentials of therapy consist in keeping the stomach empty, replenishing electrolytes and maintaining nutrition. McHardy and Browne²¹¹ report an unusual condition in a 6 year old girl in whom compression of the mesenteric arc coexisted with a duodenal bezoar.

Tuberculosis.—Migliaccio²¹² describes a lesion of the third portion of the duodenum, diagnosed histologically by competent pathologists as

207. Kautz, F. G.; Lisa, J. R., and Kraft, E.: Congenital Duodenal Obstruction, *Radiology* **46**:334-341, 1946.

208. Drucker, V.; and Cohen, E. S.: Megaduodenum Secondary to an Intrinsic Duodenal Diaphragm, *Am. J. Roentgenol.* **55**:726-729, 1946.

209. Price, S., and Chang, T.: Hepatic Abscess Complicating Atresia of the Small Intestine of a Newborn Infant, *Arch. Path.* **41**:450-453 (April) 1946.

210. Beck, W. C.: Acute Gastroduodenal Obstruction (Dilatation), *Arch. Surg.* **52**:538-546 (May) 1946.

211. McHardy, G., and Browne, D. C.: Duodenal Bezoar Resulting from Pica and Obstruction of Mesentery Artery, *J. A. M. A.* **130**:856-857 (March 30) 1946.

212. Migliaccio, A. V.: Tuberculosis of the Third-Portion of the Duodenum, *Am. J. Surg.* **71**:274-276, 1946.

tuberculosis. There was no pulmonary tuberculosis. In view of the fact that tubercle bacilli were not demonstrated microscopically or by inoculation of a guinea pig, we consider the diagnosis unproved.

Ascariasis.—Chapuy and others²¹³ describe again the curious and characteristic roentgen aspect of ascariasis in the duodenum.

Neoplasm.—Of 58 small intestinal tumors reviewed by Hoffman and Grayzel,²¹⁴ thirty-three, or 56.9 per cent, were benign and twenty-five, or 43.1 per cent, malignant. Of the benign tumors, fourteen were duodenal, eight jejunal and eleven ileal. Of the malignant tumors, four were duodenal, six jejunal and eleven ileal; in 4 instances the location was not specified. Of all tumors, 26.4 per cent were duodenal; 42 per cent of the benign and 16 per cent of the malignant tumors were duodenal. Of the fourteen benign duodenal growths, four were adenomas and six pancreatic rests, and one was a fibroma, one a lipoma, one a gastric rest and one a lymphangioma. Melena was the commonest complaint.

Three non-Vaterian carcinomas and two sarcomas of the duodenum were subjected to various surgical procedures by Brunschwig and Tiholiz.²¹⁵ One patient is alive seven years and ten months postoperatively and 1 three years postoperatively; a third lived three months, a fourth survived one year, with death after a second laparotomy for recurrence, and the fifth died seven days postoperatively.

SMALL INTESTINE

Review.—Thirty-four articles covering roentgenologic examination, tumors, inflammatory processes, deficiency states, congenital defects, chemotherapy and massive resection of the small bowel are well reviewed by Kiefer.²¹⁶

Motility.—In fasting dogs killed after various intervals of time a charcoal mixture was found by Van Liere, Stickney and Northup²¹⁷ to have traversed 54 cm. of the length of the small bowel after eight minutes, 121.2 cm. after fifteen minutes and 154.6 cm. after thirty minutes. The findings suggest that the upper half of the small intestine possesses a more active propulsive peristalsis than the lower.

213. Chapuy, A.; Naudin, and Gallavardin, L.: Un curieux aspect radiographique d'ascaridiose duodénale, *Arch. d. mal. d'app. digestif* **34**:236-238, 1945.

214. Hoffman, B. P., and Grayzel, D. M.: Benign Tumors of the Duodenum, *Am. J. Surg.* **70**:394-400, 1945.

215. Brunschwig, A., and Tiholiz, I. C.: Surgical Treatment of Malignant Tumors of the Duodenum Exclusive of Those Arising from Papilla of Vater, *S. Clin. North America* **26**:163-175, 1946.

216. Kiefer, E. D.: The Small Intestine: A Review of Recent Literature, *Gastroenterology* **5**:259-271, 1945.

217. Van Liere, E. J.; Stickney, J. C., and Northup, D. W.: The Rate of Progress of Inert Material Through the Small Intestine, *Gastroenterology* **5**:37-42, 1945.

Necheles and Olson²¹⁸ studied the effect of hemorrhage on motility in unanesthetized dogs with chronic fistulas and in dogs anesthetized with pentobarbital sodium, morphine, barbiturate or ether. Varying amounts of blood were withdrawn after a control period. The motility of the colon increased in most experiments regardless of the quantity of blood withdrawn and independent of the type of anesthesia. The motility of the stomach, gastric antrum and small intestine in most experiments either was not changed or was depressed. Stimulation, however, did occur in a number of experiments and apparently depended on the type of anesthesia.

Rapid intravenous injections of casein hydrolysate (amigen) were shown by Learner and his associates²¹⁹ to produce in anesthetized dogs a duodenal hypermotility or a change in the pattern of motility not accompanied with significant change in pH , carbon dioxide or chlorine content or total base concentration of the blood plasma. The blood glucose level was elevated. Neither the hypermotility nor the hyperglycemia was prevented by the administration of atropine or by vagotomy. Rapid intravenous injections of casein digest in unanesthetized patients changed the character of the contractions and often accentuated changes in tonus. Subjective sensations and alterations in motility were correlated in only half of the patients studied. In normal conscious dogs with Thiry's fistulas of the first portion of the jejunum distention of the fistula by means of a balloon resulted in vomiting and anorexia. Vagotomy did not abolish the vomiting or anorexia, whereas bilateral splanchnicotomy and excision of the lumbar chain did abolish the vomiting response. Unilateral denervation was not sufficient. Anorexia, however, was not abolished by this operation. Vagotomy, splanchnicotomy and section of the lumbar chains abolished both the anorexia and the vomiting. It is concluded that vomiting excited by intestinal distention is of reflex origin due to stimuli conducted over the sympathetic drain. Anorexia may result from impulses carried over both the vagi and the sympathetic nerves.²²⁰

Experiments were undertaken by Pennington, Haney and Youmans²²¹ to study in unanesthetized dogs the effect on the cardia of

218. Necheles, H.; Walker, L., and Olson, W. H.: Effect of Hemorrhage on Gastro-Intestinal Motility of Dogs: A Gradient of Gastro-Intestinal Motility, *Am. J. Physiol.* **146**:449-457, 1946.

219. Learner, N.; Robinson, H. W.; Greisheimer, E. M., and Oppenheimer, M. J.: The Effects upon Small Intestine of Rapid Intravenous Injections of Casein Hydrolysate, *Gastroenterology* **5**:201-209, 1945.

220. Herrin, R. C., and Meek, W. J.: Afferent Nerves Excited by Intestinal Distention, *Am. J. Physiol.* **144**:720-723, 1945.

221. Pennington, M.; Haney, H. F., and Youmans, W. B.: Effect of Distention of Jejunum upon Tonicity of the Cardia of the Dog, *Proc. Soc. Exper. Biol. & Med.* **62**:140-142, 1946.

distention in a segment of the jejunum (Thiry's fistula). It was found that the cardia is not easily influenced by changes in jejunal pressure. However, repeated moderate distention of a short jejunal segment may produce a decrease in tonus of the cardia, without evidence of nausea or other distress. Secondly, it was found that distention of a jejunal segment does not alter the relaxation-contraction pattern of the cardia produced by the act of swallowing or by esophageal distention.

Absorption.—While it has been known that isotonic solutions of sodium chloride introduced into the ileal segments of dogs become hypotonic within a short time, Visscher and Roepke²²² sought through experimental work to ascertain the possible effect of alteration of the osmotic activity of the blood plasma on the degree of hypotonicity so developed. After the elevation of the osmotic activity of the plasma the values for intestinal fluid did not approach the former as closely as they did before the elevation was produced. The net absorption of water was not increased in proportion to the increase in the osmotic gradient. These data add to previous evidence that although normal osmotic forces are probably contributing factors in the transport of water across the intestinal epithelium they are not the primary determinants of the direction of magnitude of the transfer.

Vitamin A tolerance curves, determined in 17 hospital control subjects by Hoffman and Dyniewicz²²³ after the ingestion of 75,000 international units of vitamin A, were slightly but significantly depressed when alumina gel was given in a 1 ounce (30 Gm.) single dose either immediately after or before the administration of vitamin A. This depression did not occur if alumina gel was given every two hours for one or more weeks before the second tolerance curve was obtained. No depression of the curve was noted when aluminum phosphate gel was used in place of alumina gel. In 33 patients with peptic ulcer given alumina gel for two or more weeks the concentration of vitamin A and carotene in the plasma showed no deviation from normal. Therapeutic doses of alumina gel (or aluminum phosphate gel) have no demonstrable effect on the absorption of amino acids, ascorbic acid, glucose and neutral fats.²²⁴

The administration of succinylsulfathiazole for five days (0.25 Gm. per kilogram per day) did not decrease the area of intestinal gas shadows

222. Visscher, M. B., and Roepke, R. R.: Influence of Induced Changes in Blood Plasma Osmotic Activity on Intestinal Absorption, *Proc. Soc. Exper. Biol. & Med.* **60**:1-4, 1945.

223. Hoffman, W. S., and Dyniewicz, H. A.: The Effect of Alumina Gel upon the Absorption of Vitamin A from the Intestinal Tract, *Gastroenterology* **5**:512-522, 1945.

224. Hoffman, W. S., and Dyniewicz, H. A.: The Effect of Alumina Gel upon the Absorption of Amino Acids, Ascorbic Acid, Glucose, and Neutral Fat from the Intestinal Tract, *Gastroenterology* **6**:50-61, 1946.

in normal subjects at sea level, as studied in roentgenograms by Raspberry.²²⁵ After three days of administration of the drug, however, most subjects experienced less discomfort on ascent to a simulated altitude of 36,000 feet (11,887 meters); this was attributed to greater ease in expulsion of the gas, due to an increased fluidity of the contents of the bowel.

Tuft and Tumen²²⁶ report 5 cases illustrating a clinical syndrome ascribed to intolerance to fats and sugars. The symptoms include fullness, discomfort, belching, eructation, heartburn, flatulence, cramplike pains and irregularities of the bowel, consisting chiefly in attacks of diarrhea. These symptoms are clearly those of dysfunction of the bowel, whether due to intolerance to fats and sugars as the authors suggest by a mechanism admittedly not well understood or to some other process. It may be difficult to distinguish between an abnormal response to normal irritants and "intolerance." Studies of tolerance to glucose and fat in such cases should be of interest.

Diverticula.—In two and a half years 25 cases of diverticulosis of the jejunum and ileum were noted at the Boston City Hospital. Most of the patients were in middle or late life, 1 being in the third decade, 3 in the fifth decade and 21 over 60 years of age. In 20 patients the condition was jejunal, in 4 it was in both ileum and jejunum and in 1 it was in the ileum. In 10 there was a single diverticulum, 10 had two to four diverticula and 5 had five or more diverticula. The association with symptoms was not clear, but 22 had vague abdominal distress. Eleven had associated duodenal diverticula (44 per cent), 6 had associated diverticula of the colon (24 per cent), 5 had esophageal hiatus hernia (20 per cent) and only 1 had esophageal diverticula.²²⁷

Klidjian²²⁸ reports a painless severe rectal hemorrhage lasting twenty-four hours. At operation eight diverticula were found in a 35 cm. segment of the proximal jejunum, the first one being situated 10 cm. from the duodenojejunal flexure. The largest one, 3.8 cm. in diameter, contained a hard stone. Resection of the affected loop with an end to end anastomosis was made. The source of the bleeding was not demonstrated.

A 53 year old woman seen by Shutkin²²⁹ complained of steady severe pain in the upper abdominal and left periumbilical areas, followed by

225. Raspberry, E. A., Jr.: The Effect of Succinylsulfathiazole on the Volume of Intestinal Gas in Normal Young Men, *Gastroenterology* 5:175-180, 1945.

226. Tuft, L., and Tumen, H. J.: Fat and Sugar Intolerance as Cause of Gastrointestinal Symptoms, *J. A. M. A.* 130:624-627 (March 9) 1946.

227. Ritvo, M., and Votta, P. J.: Diverticulosis of the Jejunum and Ileum, *Radiology* 46:343-350, 1946.

228. Klidjian, A.: Jejunal Diverticulosis Complicated by Haemorrhage, *Brit. M. J.* 1:683-684, 1946.

229. Shutkin, M. W.: Diverticulitis of the Jejunum with Perforation, *Gastroenterology* 5:102-105, 1945.

vomiting. Two weeks later a similar attack occurred. The author saw the patient in the third attack. The temperature was 100 F. and the leukocyte count 15,650, with 91 per cent polymorphonuclear cells; the abdomen was distended and tympanitic; the skin of the left side of the navel was hyperesthetic. Roentgenologic examination revealed three diverticula in the proximal part of the jejunum. Ten days later the patient was hospitalized, with recurrent symptoms, and laparotomy revealed a perforated diverticulum the size of a walnut.

Meckel's Diverticulum.—An analysis of 61 cases of Meckel's diverticulum from 1934 to 1944 at Duke Hospital by Howell²³⁰ disclosed these facts: The incidence of the anomaly was less than 0.1 per cent. The average duration of symptoms in acute diverticulitis was forty-nine and one-tenth hours; characteristically the patient had abdominal pain, at first periumbilical and later localizing in the right lower abdominal quadrant; nausea was usually present without vomiting. Intestinal bleeding occurred in 10 per cent of the instances of diverticula. In only 12 per cent were the symptoms diagnosed correctly preoperatively; in 60 per cent the diagnosis was appendicitis. Aberrant gastric mucosa was present in 24.6 per cent.

Atwood²³¹ reports an invaginated Meckel's diverticulum resulting in death; Grattan²³² describes a fatal case of gangrene.

On the basis of 4 new cases and a review of the literature, Lund²³³ discusses peptic ulcer of Meckel's diverticulum. Emphasis is laid on profuse periodic rectal hemorrhages and a tendency to perforate, the latter present in 60 per cent of the known cases.

Hemorrhage.—Jones²³⁴ reports 4 cases of obscure hemorrhage in which the patients were found to have, respectively, congenital anomaly of the intestine with heterotopic gastric mucosa and chronic diffuse enteritis, an ulcer of Meckel's diverticulum, an ulcerated leiomyofibroma in the jejunum and a large Meckel's diverticulum resembling a miniature stomach the size of an orange.

Massive hemorrhage occurring three weeks after shrapnel injury and surgical repair of jejunal perforations is reported by Hawkes and

230. Howell, L. M.: Meckel's Diverticulum, *Am. J. Dis. Child.* **71**:365-377 (April) 1946.

231. Atwood, W. G.: Meckel's Diverticulum, *New England J. Med.* **234**:329-332, 1946.

232. Grattan, D. A.: A Case of Gangrene of Meckel's Diverticulum, *Brit. M. J.* **2**:85, 1945.

233. Lund, J.: L'ulcere peptique du diverticule de Meckel, *Acta chir. Scandinav.* **92**:291-307, 1945.

234. Jones, T. E.: Management of Obscure Gastrointestinal Hemorrhage, *Ohio State M. J.* **42**:361-364, 1946.

Spencer.²³⁵ In twenty-four hours the patient received 14,500 cc. of transfused blood. Recurrent bleeding the following week necessitated the administration of 35 pints of blood (17,500 cc.) in addition to other fluids. The patient recovered after excision of the segment of jejunum previously repaired; a large bleeding vessel was found in an eroded area.

In hemorrhage clinically considered to be due to Henoch's purpura the first portion of the jejunum, according to Whitmore and Peterson,²³⁶ appeared roentgenologically to be dilated with irregularities of the mucosal outline, resembling small diverticula or ulcers. The process involved 25 cm. of the upper jejunum. A roentgenogram one month later showed much improvement.

Paralytic Ileus.—Bastenie,²³⁷ in an interesting paper, describes the intestinal disturbances manifested in 29 cases of severe hypothyroidism, 10 of which came to autopsy. These disturbances varied from simple constipation to megacolon and from abdominal distention to intestinal obstruction. When present, intestinal paresis appeared gradually; spontaneous defecation was absent for as long as a week, flatus was rarely passed and enemas produced only a few scybala. Roentgenograms revealed distended loops of bowel, sometimes with fluid levels. In some cases the onset was so rapid as to suggest the presence of a cyst or tumor. Thyroid therapy was not effective if begun too late.

Mechanical Ileus.—Wangensteen,²³⁸ in an excellent paper, reviews the clinical aspects of the problem of intestinal obstruction. Drake²³⁹ reports another instance of high obstruction, produced by a faceted gallstone, 2.5 by 2.5 by 3 cm. in diameter, in the jejunum. Russell²⁴⁰ emphasizes the value of colonic irrigation as a diagnostic and therapeutic procedure. He also calls attention again to the old observation that on digital examination the mechanically obstructed bowel may be found collapsed against the examining finger whereas in paralytic ileus the rectal ampulla is usually dilated.

Moses,²⁴¹ in a review of 118 cases of acute intestinal obstruction seen in a large hospital from Jan. 1, 1943 to March 1, 1945, found that

235. Hawkes, S. Z., and Spencer, R. F.: Repeated Massive Intestinal Hemorrhages: Report of an Unusual Case, *Ann. Surg.* **123**:1063-1066, 1946.

236. Whitmore, W. H., and Peterson, G. M.: Henoch's Purpura: Small Intestinal Changes, *Radiology* **46**:373-376, 1946.

237. Bastenie, P. A.: Paralytic Ileus in Severe Hypothyroidism, *Lancet* **1**: 413-416, 1946.

238. Wangensteen, O. H.: Clinical Aspects of the Bowel Obstruction Problem, *Canad. M. A. J.* **54**:234-242, 1946.

239. Drake, C. B.: Gallstone Ileus, *Minnesota Med.* **29**:330-331, 1946.

240. Russell, T. H.: Intestinal Obstruction, *S. Clin. North America* **26**:382-389, 1946.

241. Moses, W. R.: Acute Obstruction of the Small Intestine, *New England J. Med.* **234**:78-82, 1946.

the mortality rate for 18 patients not operated on was the same as it was for 90 who were operated on (8 per cent). Immediate operation led to poorer results than delay, provided vigorous preoperative therapy was given. Moses concludes that surgical intervention should be postponed until the pulse rate is stabilized below 110, the blood pressure at least near normal, the acid-base balance restored, hydration achieved, the definitive treatment of complications under way and the general effects of shock alleviated. Zeitlen and Mazel²⁴² discuss the dangers attendant on the improper use of the Miller-Abbott tube.

Barney and others,²⁴³ in a study of 221 soldiers with abdominal wounds contaminated with feces who survived and returned to civilian life, found that in 12.6 per cent obstruction developed later. All types of obstruction of the small bowel were encountered, including fixed kinks, closed loops, traction volvulus and internal herniation. The history of an abdominal wound received in war, the presence of scars in the abdomen and the rapid onset of cramplike abdominal pain with nausea and vomiting constitute the clinical picture. The treatment advised is early operation. The routine use of the Miller-Abbott tube is not favored because of the high incidence of strangulation. Colonic obstruction is best treated by decompression, correction of fluid and electrolyte balance and one stage resection or anastomosis of the bowel.

Intra-Abdominal Bands.—Larson²⁴⁴ describes 3 instructive cases of partial intermittent intestinal obstruction, due in 2 to intraperitoneal bands of unknown origin without previous celiotomy or injury.

Internal Hernia.—Hollenberg²⁴⁵ reports the first case on record of a hernia through the foramen of Winslow, wherein a preoperative diagnosis was established from the roentgenologic investigation. The right half of the transverse colon, ascending colon and cecum were involved. The tip of the appendix was seen high under the liver.

Ravdin and Hodes²⁴⁶ report a retroperitoneal hernia involving a small portion of the distal ileum. The thin, transparent and avascular sack also contained Meckel's diverticulum, causing the obstructive symptoms. Preoperative roentgenologic studies pointed to the correct diagnosis. Surgical treatment, with complete resection and anastomosis,

242. Zeitlen, N. S., and Mazel, M. S.: Intestinal Obstruction: Further Experience in the Use of Flat Abdominal Films, *Radiology* **45**:267-277, 1945.

243. Barney, C. O.; Roettig, L. C., and Jones, G. F.: Mechanical Intestinal Obstruction Following War Wounds of the Abdomen, *M. Clin. North America* **30**:337-347, 1946.

244. Larson, E. E.: Intra-Abdominal Bands in the Scarless Abdomen, *West. J. Surg.* **54**:177-182, 1946.

245. Hollenberg, M. S.: Radiographic Diagnosis of Hernia into the Lesser Peritoneal Sac Through the Foramen of Winslow, *Surgery* **18**:498-502, 1945.

246. Ravdin, I. S., and Hodes, P. J.: Retroperitoneal (Mesenteric Pouch) Hernia: Case Report, *Ann. Surg.* **123**:106-110, 1946.

was successful. The herniation consisted of a trapped portion of the ileum lying behind a mesenteric veil of the ascending colon. Apparently, in the primary rotation of the intestine and the subsequent movement of the large bowel to the right and downward the involved portion of small intestine became imprisoned between the mesentery and the colon.

Paraduodenal Hernia.—The 2 cases of paraduodenal hernia seen at the Lahey Clinic in the past nineteen years are reported by Lahey and Trevor,²⁴⁷ who warn that in every patient with unexplained and persistent abdominal symptoms the region of the ligament of Treitz should be included in the general exploration of the abdomen.

Intussusception.—Smith²⁴⁸ describes 35 cases of intussusception, in 31 of which the patients were subjected to operation, with a mortality of 16.1 per cent. There were 24 males and 11 females, with ages ranging from 5 weeks to 60 years. The ileocecal or ileocolic variety was found in 50 per cent of the entire group. Nausea, vomiting, pain and a palpable abdominal mass were the most constant symptoms. In 3 cases rectal examination disclosed masses not palpable in the abdomen. Surgical therapy consisted in a reduction of the intussusception from below upward except in the 8 cases in which resection was done. The incidence of recurrent intussusception was low.

Volvulus.—Tiscenco²⁴⁹ presents a detailed roentgen description of subacute volvulus of the terminal ileum. The continuity of the normal mucosal folds with those of the stenosed segment was demonstrated; at the junction they resembled a twisted and kinked ribbon. The preserved contractibility and smoothness of the strictured lumen, the integrity of the mucosal folds and the spontaneous unfolding of the most twisted segment after a barium meal were noteworthy. Operation disclosed evidence of a recurring incomplete volvulus of the terminal ileum due to congenital absence of proper mesenteric fixation.

Seven cases of volvulus of the small intestine in East African natives are described by Kerr and Kirkaldy-Willis.²⁵⁰ One patient had diarrhea and another passed blood and mucus by rectum. The duration of symptoms varied from one hour to four days. Reduction was carried out by exteriorization and rotation until the mesentery lay straight. The bowel was emptied by open enterostomy. The abdomen was not drained. There were no adhesions or other apparent cause within the abdomen

247. Lahey, F. H., and Trevor, W.: Right Paraduodenal Hernia, *Ann. Surg.* **122**:436-443, 1945.

248. Smith, O. F.: Intussusception—Diagnosis and Treatment, *Am. J. Surg.* **70**:158-163, 1945.

249. Tiscenco, E.: Subacute Volvulus of the Terminal Ileum, *Brit. J. Radiol.* **19**:243-247, 1946.

250. Kerr, W. G., and Kirkaldy-Willis, W. H.: Volvulus of the Small Intestine, *Brit. M. J.* **1**:799-800, 1946.

for the rotation except in a case in which two tapeworms, each 4 feet (121.9 cm.) long, were found tied together in a massive knot at the upper end of the jejunum. Two of the cases were complicated by rotation of the cecum and ascending colon; in 1 an accompanying volvulus of the pelvic colon was discovered after reduction of the volvulus of the small intestine. There was 1 death from peritonitis. The reduction in mortality rate is attributed to the postoperative use of gastric suction and the intravenous injection of isotonic solution of sodium chloride. The practice of the African native of taking large gruel meals is considered to be the factor responsible for the development of the volvulus.

Postirradiation Stricture.—Saltzstein²⁵¹ reports an instance of intestinal obstruction due to adhesions following prolonged roentgenologic therapy for carcinoma of the fundus uteri.

Scleroderma.—In a patient with scleroderma, Pugh, Kvale and Margulies²⁵² noted roentgenologically stiffness of the esophagus with an absence of peristalsis. In the small intestine peristalsis was sluggish and contractibility diminished. These abnormalities, together with the pulmonary changes present, were interpreted as visceral manifestations of scleroderma.

Intestinal Tuberculosis.—Adams and Miller²⁵³ present their experience in the surgical treatment of intestinal tuberculosis in 19 patients. Abdominal fistulas were closed in 4 patients, with recurrence in 3; the closure was maintained at least three and a half years in the fourth. Resection of the right side of the colon, with formation of a Mikulicz ileotransverse colostomy and secondary closure was done in 7; in 1 there was coexisting adenocarcinoma, with death two and a half years later from carcinomatosis. Four patients did well from nine months to three and a half years later; in 1 recurrence resulted in death four years after the initial operation. Resection of the right side of the colon with primary ileocolic anastomosis was accomplished in 3 cases, with postoperative death in 1. In two segmental resections of small bowel with primary anastomoses the patients experienced a recession of symptoms for one year. Two side-tracking ileotransverse colostomies were done, with death occurring twelve days later in 1 and seven months later in the other. One resection of the sigmoid resulted in a painful abscess, treated by permanent colostomy; a draining perineal sinus persisted for two years, but pain was relieved.

251. Saltzstein, H. C.: Small Bowel Stricture Following Irradiation Therapy for Carcinoma of the Fundus Uteri, *Surgery* **18**:556-560, 1945.

252. Pugh, D. G.; Kvale, W. F., and Margulies, H.: Scleroderma with Involvement of the Viscera: Report of a Case, *Proc. Staff. Meet., Mayo Clin.* **20**: 410-414, 1945.

253. Adams, R., and Miller, W. H.: Surgical Treatment of Intestinal Tuberculosis, *S. Clin. North America* **26**:656-664, 1946.

Taylor²⁵⁴ describes 3 cases of hypertrophic ileocecal tuberculosis; in 1 chronic tuberculous mesenteric lymphadenitis was present with ileal changes similar to those characteristic of Crohn's disease.

Regional Enteritis.—Several interesting studies of regional enteritis have been reported. In Brown's²⁵⁵ 12 cases no pathognomonic symptom complex was found. Most of the lesions were in the terminal ileum, but some were in the jejunum and even the duodenum. The roentgenologic signs in order of importance were as follows: deformity of the contour, narrowing of the lumen, hourglass constriction, loss of mucosal pattern, rigidity and immobility, internal fistulous tracts, malposition of neighboring intestine, hypermotility and stenosis. In all cases surgical treatment was used; in three recurrences roentgenologic therapy was tried with remarkable results.

An analysis of 17 cases by Pugh²⁵⁶ disclosed the following incidence of symptoms: pain in 16 cases; diarrhea, loss of weight and anemia in 7 cases; obstruction in 3 cases, and hemorrhage in 1 case. Among the findings, leukocytosis occurred in 17, Kantor's string sign in 10, extension to the colon on roentgenologic study in 9, internal fistula in 6, external fistula in 4 and "skip areas" in 3.

In 3 cases the disease was managed medically successfully, 2 patients receiving penicillin. Among 14 surgically treated patients, there was 1¹ fatality. The cause was not determined, though sensitivity to sulfonamide drugs was suspected. A one stage procedure was employed in 12 cases. In 3 of the patients subjected to operation penicillin was used, with apparently beneficial effects.

In two years Asencio-Camacho²⁵⁷ performed fifteen resections for acute regional enteritis in Puerto Rico. The clinical impression was usually acute appendicitis or mesenteric lymphadenitis. Hyperplastic lymphadenopathy with diffuse submucosal edema and intense cellulitis with dilatation of the lymphatics was noted in 8 cases. "Skip lesions" were present in 3 and tubular fibrotic stenosing enteritis in 4. The author considers regional enteritis to be a functional disorder of the lymphatic system, giving rise to phases of hyperplasia, "skip lesions" and intestinal fibrosis.

The series reported by Kiefer and Ross²⁵⁸ consists of 102 cases, in 11 of which the disease was in the acute stage. Pain was the most

254. Taylor, A. W.: Chronic Hypertrophic Ileocecal Tuberculosis and Its Relation to Regional Ileitis (Crohn's Disease), *Brit. J. Surg.* **33**:178-181, 1945.

255. Brown, S.: Chronic Nonspecific Regional Enteritis, *Am. J. Roentgenol* **54**:487-497, 1945.

256. Pugh, H. L.: Regional Enteritis, *Ann. Surg.* **122**:845-861, 1945.

257. Asencio-Camacho, F.: Regional Enteritis in Puerto Rico, *Gastroenterology* **6**:493-503, 1946.

258. Kiefer, E. D., and Ross, J. R.: Criteria in the Management of Chronic Ileitis, *J. A. M. A.* **129**:104-108 (Sept. 8) 1945.

frequent symptom and diarrhea the second most frequent. Ileocolostomy without resection was unsatisfactory in complicated cases. The operative mortality in ileoascending colectomy was remarkably low. It is concluded that conservative management is indicated in the early acute forms of the disease, in mild chronic uncomplicated terminal ileitis and in uncomplicated segmental enteritis with extensive involvement of the jejunum and ileum; chronic terminal ileitis is best treated surgically. Tomaszewski ²⁵⁹ gives a general review of the subject.

Inberg describes ²⁶⁰ "a new symptom of ileitis," a referred pain in the right flank on both sides of the highest point of the iliac crest and in the iliac fossa close to the bone; he suggests that the pain is of a neurologic nature, subsequent to lymphadenitis secondary to Crohn's disease and affecting the narrow zone in the flank where the iliohypogastric and ilioinguinal nerves lie near the surface. Diagnostic analgesia relieves the pain. We are not favorably impressed by the description.

Several case reports are of interest. The patient described by Einhorn and Pickhardt ²⁶¹ had vague symptoms of intestinal obstruction and a palpable abdominal mass; cure was effected by resection of extensive segments of the ileum and sigmoid. Extensive involvement of the upper part of the jejunum and terminal segment of the ileum was treated by Gendel and Beaver ²⁶² with a one stage resection and anastomoses. The proximal portion of the jejunum was involved (18 inches [50.8 cm.]), beginning approximately 12 inches (30.5 cm.) from the ligament of Treitz. This was resected. Approximately three months later spontaneous perforation of the jejunum (not in the line of resection) necessitated a laparotomy; an abscess was evacuated, and the involved segment of jejunum was resected. Penicillin, 2,750,000,000 units, was administered in a period of two weeks. In August 1946, four months after the initial operation, the patient was discharged, having gained 44 pounds (20 Kg.) in weight. In Mazel's ²⁶³ patient the atypical symptoms were suggestive of steatorrhea. In Koenig's ²⁶⁴ case of chronic jejunitis there were numerous tubercle-like granulomas in association with a considerable amount of foreign material. No etiologic agent could be established.

259. Tomaszewski, C. A.: Forma cronica de enteritis regional, *Rev. Asoc. méd. argent.* **60**:302-306, 1946.

260. Inberg, K. R.: Indefinite Pain in the Right Flank and Its Origin—A New Symptom of Ileitis, *Acta chir. Scandinav.* **93**:213-230, 1946.

261. Einhorn, M., and Pickhardt, O. C.: Observation d'un cas de jéjuno-iléite segmentaire, *Arch. d. mal. de l'app. digestif* **34**:112-117, 1945.

262. Gendel, S., and Beaver, M. G.: Non-Specific Regional Jejunitis, *Am. J. Surg.* **71**:374-380, 1946.

263. Mazel, M. S.: Regional Ileitis: Report of an Asymptomatic Lethal Case, *Am. J. Surg.* **71**:412-419, 1946.

264. Koenig, A. S.: Chronic Jejunitis, *Arch. Path.* **40**:187-190 (Sept.) 1945.

Bennett²⁶⁵ reports 2 cases in which a palpable mass in the right lower abdominal quadrant brought the patient to laparotomy. One of these is particularly instructive. At operation a preliminary short-circuiting operation was done because of a "tumor" involving the cecum and the lower 3 inches (7.6 cm.) of the ileum. When the abdomen was opened later for the second stage, the "tumor" previously noted was not in evidence, the involved parts being entirely normal. Two years later the patient, a woman aged 39, was in good health. The occasional reports of such instances suggest that resolution takes place in this disease much more frequently than has been realized heretofore.

In a boy with normal development to the age of 13 anorexia, loss of weight and abdominal cramps began to develop. Secondary sex characteristics were absent at the age of 17 when he was first seen by Alvarez.²⁶⁶ A roentgenogram revealed a stenosing hyperplastic ulcerating enteritis of the upper part of the jejunum. At operation 5 feet (152.4 cm.) of involved intestine was removed. Adult physical characteristics appeared after operation, but severe ulcerative colitis developed. We note that more and more cases of regional enteritis and ulcerative colitis occurring concomitantly or in sequence in the same person are being seen and reported, thus suggesting an etiologic relationship in spite of the different pathologic manifestations.

Benign Tumors.—Baker and Halley²⁶⁷ report two neurofibromas, with recurrent intestinal bleeding as the chief symptoms. In severe intestinal hemorrhage of undetermined cause, with bright red blood in the stool, a search should be made for a benign tumor of the small bowel.

Endometriosis.—Wood and others²⁶⁸ describe a 38 year old woman with attacks of pain in the lower area of the abdomen coinciding with the menstrual periods, shown at operation to be due to endometriosis involving 3 inches (7.6 cm.) of the ileum.

Carcinoids.—Two carcinoids of the ileum, one with symptoms suggestive of recurrent appendicitis and the second with partial obstruction of the bowel, are reported by Reynolds and Cantor.²⁶⁹ There were no metastases. In the case described by McNeely and Jones²⁷⁰ multiple

265. Bennett, A. H.: Crohn's Disease, *Lancet* **1**:846-847, 1946.

266. Alvarez, W. C.: Stoppage of Bodily Growth in a Boy with Stenosing Enteritis, *Gastroenterology* **5**:281-282, 1945.

267. Baker, H. L., and Halley, H.: Neurofibroma of the Small Intestine with Massive Hemorrhage, *Ann. Surg.* **123**:1067-1073, 1946.

268. Wood, O. T.; Deibert, I., and Kain, T.: Endometriosis Causing Intestinal Obstruction, *J. A. M. A.* **130**:341-343 (Feb. 9) 1946.

269. Reynolds, R. P., and Cantor, M. O.: Surgical Importance of Carcinoid Tumors of the Ileum, *Am. J. Surg.* **71**:705-709, 1946.

270. McNeely, R. G. D., and Jones, N. W.: Secondary Pellagra Caused by Multiple Argentaffin Carcinoma of the Ileum and Jejunum, *Gastroenterology* **6**: 443-448, 1946.

growths of the small intestine, with the typical histologic picture of a malignant carcinoid tumor and secondary involvement of the regional lymph nodes and liver, were found at autopsy in a patient with the classical clinical picture of pellagra, including pigmentation of the skin, lesions of the mouth and tongue and edema of the intestine. The stools contained no fat.

Dickson and others²⁷¹ report a carcinoid of the ileum, with a large retroperitoneal metastasis and extensive involvement of the mesentery. The primary lesion of the ileum was resected. The authors reemphasize the fact that carcinoid tumors must be regarded as carcinomas of slow growth and low grade malignant nature.

Carcinoma.—Thirty-eight consecutive cases of verified primary malignant disease of the small intestine are reviewed by Shallow, Eger and Carty,²⁷² who add a case of a jejunal carcinoma producing a contact fistula to the terminal ileum. Three per cent of intestinal carcinomas and 60 per cent of intestinal sarcomas occur in the small intestine. Sarcoma is commoner in the ileum and carcinoma least frequent there. The operative mortality is 44 per cent, highest in duodenal lesions and lowest in the jejunal group. Two cases are added by Emmett and Dreyfuss,²⁷³ and 1 is added by Mulligan²⁷⁴ in which there was associated hyperplasia of the parathyroid glands and generalized osteoporosis.

Sarcoma.—Berman and Mainella²⁷⁵ found in the literature detailed follow-up studies of 103 patients with lymphosarcoma of the intestine; of these, 14 (13.6 per cent) survived five years or more. A report of a case in which there was a five year survival is presented, and the records of 2 other such cases are briefly discussed.

Twenty-one cases of lymphoblastoma of the small intestine were found by Fryfogle, Kiernan and Dockerty²⁷⁶ to originate in single small follicles of the small bowel. These follicles are plentiful in the

271. Dickson, J. A.; Parkhill, E. M., and Kiernan, P. C.: Large Retroperitoneal Metastasis from a So-Called Carcinoid of the Small Intestine, *Surg., Gynec. & Obst.* **82**:675-681, 1946.

272. Shallow, T. A.; Eger, S. A., and Carty, J. B.: Primary Malignant Disease of the Small Intestine, *Am. J. Surg.* **69**:372-383, 1945.

273. Emmett, J. M., and Dreyfuss, M. L.: Malignant Tumors of the Small Bowel, *Ann. Surg.* **123**:859-865, 1946.

274. Mulligan, R. M.: Adenocarcinoma of the Jejunum Associated with Hyperplasia of the Parathyroid Glands and Generalized Osteoporosis, *Arch. Path.* **40**:182-186 (Sept.) 1945.

275. Berman, H., and Maimella, F.: Lymphosarcoma of the Small Intestine, *Am. J. Surg.* **70**:121-125, 1945.

276. Fryfogle, J. D.; Kiernan, P. C., and Dockerty, M. B.: Lymphoblastoma of the Small Intestine: Case Report, *Proc. Staff Meet., Mayo Clin.* **21**:161-169, 1946.

ileum, fewer in the jejunum and almost nonexistent in the duodenum. Abdominal pain and low grade intestinal obstruction were the commonest symptoms. Prognosis from the histologic appearance was not possible.

Mascheroni and others²⁷⁷ report a lymphosarcoma of the ileum.

APPENDIX

Incidence of Appendectomy.—Stiles and Mulsow²⁷⁸ found that 10 per cent of 2,968 college students had undergone appendectomy at some previous time.

Acute Appendicitis.—O'Connor²⁷⁹ made a statistical study of 2,000 cases of appendicitis. The position of the appendix was found to be retrocecal in 23.4 per cent, retroperitoneal in 3.4 per cent and medial to cecal or pelvic in location in 73.6 per cent. The pathologic changes were of the acute catarrhal suppurative type in 56.90 per cent and of the gangrenous type in 5.90 per cent; the appendix was ruptured in 6.55 per cent. In 587 cases, or 29.35 per cent of the entire series, chronic appendicitis was evident; in 7.3 per cent no disease was found. In the postoperative treatment sulfonamide drugs were given either by mouth or by vein or both in 108 cases (8.5 per cent) and intraperitoneally during operation in 87 per cent. The mortality was 54 cases, or 0.25 per cent. O'Connor emphasizes the value of sulfonamide drugs in adequate dosage intraperitoneally with liberal use of Wangensteen drainage and intravenous injection of fluids.

The mortality in Lyall's²⁸⁰ 480 consecutive cases was 0.5 per cent with the use of sulfonamide powder intraperitoneally.

Norris²⁸¹ reviews 1,000 cases of appendicitis in children seen over a twenty year period. Abdominal pain, nausea and vomiting and fever were the chief complaints. The white blood cell count averaged 16,700, varying from 3,100 to 60,000. Tenderness in the right lower abdominal quadrant was present in 989 and rigidity in 681. The process was acute in 667 cases; in 416 of these appendectomy was performed before perforation occurred. The over-all mortality was 3.2 per cent (1,000). There were no deaths in 246 elective cases, 1.15 per cent mortality in 87

277. Mascheroni, H. A.; Reussi, C., and Clerici, L. E.: Linfo-sarcoma del ileon, Rev. Asoc. méd. argent. **60**:330-333, 1946.

278. Stiles, K. A., and Mulsow, F. W.: Incidence of Appendicitis from a Survey of College Students, Am. J. Digest. Dis. **13**:39-40, 1946.

279. O'Connor, H. A. D., and Bessie, E. M.: Appendicitis: A Survey of the Last Two Thousand Consecutive Cases, New York State J. Med. **45**:1535-1538, 1945.

280. Lyall, A.: Treatment of Acute Appendicitis: A Study of Four Hundred and Eighty Consecutive Cases, Brit. M. J. **2**:719-721, 1945.

281. Norris, W. J.: Appendicitis in Children: Review of One Thousand Cases, West. J. Surg. **54**:183-192, 1946.

cases of subacute disease, 4.65 per cent mortality in 667 cases of acute disease and 10.76 per cent mortality in 251 cases of acute disease with perforation. Delay in the hospitalization of patients was the greatest cause of mortality and morbidity. The sulfonamide drugs were the most important factor in the reduction of the mortality. Postoperative pneumonia was the commonest cause of death before 1939.

In eighteen months 1,500 appendectomies, with only 1 death, were carried out by Crile and Fulton²⁸²; 65 per cent of the patients had true acute appendicitis. Early diagnosis, the health and youth of the patients and the fact that only an occasional patient had taken a cathartic after the onset of symptoms were important factors in the low mortality. Chemotherapy with penicillin and antibiotics was of great value in controlling infection. Most patients with symptoms for forty-eight hours or more were treated conservatively, operation being deferred for a month or more. Gastric suction and Miller-Abbott intubation were used when needed. In complicated cases penicillin was given in doses of 100,000 units every two hours intramuscularly.

Unusual Forms and Complications.— Babcock²⁸³ directs attention to a variety of unusual types of appendicitis with atypical clinical manifestations. Posterior or retrocecal appendicitis often lacks the intense local tenderness and rigidity present when the organ is close to the anterior abdominal wall. Inflammation of an appendix located in the pelvis is characterized by epigastric distress and nausea, followed by fever and leukocytosis but without either rigidity or tenderness at McBurney's point. The appendix not infrequently is found in a hernial sac, particularly that of an inguinal hernia on the right side. The absence of the tense, distended sac differentiates the condition from the usual strangulated hernia. The signs and symptoms of lumbar appendicitis are striking and characteristic. The attack begins, as in the usual form of appendicitis, with epigastric distress, nausea, moderate fever, elevation of the pulse rate and polymorphonuclear leukocytosis. The pain, tenderness and rigidity, however, localize in the lumbar muscles on the right above the crest of the ileum. The patient may complain of pain and tenderness in the anterior surface of the right thigh, in the right scrotum or, in the female, in the right labium majus. There also may be vesical irritability and hematuria. A degree of lumbar scoliosis with concavity to the right may develop, and later, from the inflammatory exudate, the margins of the right psoas muscle may appear blurred on roentgenologic examination. Occasionally, from a retrocecal or pelvic

282. Crile, G., Jr., and Fulton, J. R.: Appendicitis with Emphasis on the Use of Penicillin, U. S. Nav. M. Bull. **45**:464-473, 1945.

283. Babcock, W. W.: Unusual Types of Appendicitis, Pennsylvania M. J. **49**:728-732, 1946.

appendix a persistent sinus forms or recurrent abscesses develop until the appendix is removed. Persistent or recurrent discharging sinuses having a course anywhere near a possibly diseased appendix should be investigated as of possible appendical origin. Most of the appendix may have been removed previously through operation or necrosis, yet a small portion with mucous lining, a fecal concretion, a nonabsorbable suture or ligature or other foreign body may be responsible for persistence of the sinus.

Rubenstein and Johnson²⁸⁴ discuss 20 cases presenting the signs and symptoms of acute appendicitis in conjunction with salmonella infection; 18 came to operation. Histopathologic examinations disclosed evidence of acute, subacute or gangrenous appendicitis in 7 and no acute inflammation in 11. Review of the preoperative studies was not helpful in seeking a method for the differentiation of one group from the other. Five different varieties of *Salmonella* were found in the 17 cases in which the organism was typed. *Salmonella typhi* murium and *S. newport* were isolated in cases of acute inflammation of the appendix and in cases without such inflammation. In all 6 cases of infection with *S. paratyphi* involvement of the lymphoid tissue of the appendix or mesenteric nodes was the most significant pathologic process. An unexplained fever after appendectomy should raise the question of underlying infection with *Salmonella*.

Gilje and Lampson²⁸⁵ report acute appendicitis associated with active amebic dysentery.

Ravdin and North²⁸⁶ observed 13 patients with coexistent malaria and symptoms of acute appendicitis; in 10 the appendix was found to be acutely inflamed. The authors conclude that if the signs and symptoms suggest an acute condition within the abdomen requiring surgical treatment it is safer not to delay operation too long unless prompt improvement follows antimalarial therapy.

Greene²⁸⁷ reports an instance of infectious mononucleosis simulating a surgical emergency for appendicitis.

Haddon²⁸⁸ describes a fatal instance of appendicitis involving the left side. The small bowels was confined to the right side, and the cecum and the ascending and descending colon occupied the left. Capone and Mil-

284. Rubenstein, A. D., and Johnson, B. B.: *Salmonella* Appendicitis, *Am. J. M. Sc.* **210**:517-523, 1945.

285. Gilje, L. E., and Lampson, R. S.: *Acute Appendicitis in Amebic Dysentery*, *U. S. Nav. M. Bull.* **46**:109-111, 1946.

286. Ravdin, I. S., and North, John P.: *The Simultaneous Occurrence of Acute Appendicitis and Malaria*, *Ann. Surg.* **122**:432-435, 1945.

287. Greene, M. J.: *Infectious Mononucleosis Simulating Acute Appendicitis*, *Mil. Surgeon* **98**:400-401, 1946.

288. Haddon, J. W. L.: *A Case of Left-Sided Appendicitis*, *Brit. M. J.* **2**: 569, 1945.

ler²⁸⁹ report a similar instance with dextrocardia in a 10 year old boy, with operative recovery.

Courty²⁹⁰ reports an instance of appendicitis with pelvic peritonitis in which the periappendicular inflammatory reactions simulated recto-sigmoidal cancer.

Roque Suárez²⁹¹ reports 2 cases of diverticulosis of the appendix: In the first, acute appendicitis was present and the diverticulum was an incidental finding; in the second, pain in the right lower abdominal quadrant, diagnosed as "chronic appendicitis," had existed for one year and the diverticulum was the only abnormality found at operation.

Bergeret and Cotillon²⁹² give an excellent discussion of appendicular invagination, with a report of 11 cases. Intussusception of the appendix into itself, the third instance to be reported in the literature, is described by Ingersoll and Meigs.²⁹³ It was preceded, apparently, by an attack of acute appendicitis.

In the appendixes of 898 patients studied by White and Ellis²⁹⁴ one polyp (0.11 per cent) was noted. Familial polypoid hypertrophy of the mucosa and reactive hyperplasia following prolonged inflammation are suggested as possible factors of pathogenesis.

Alecha and Deluchi-Levene²⁹⁵ report an epithelioma of the appendix.

Morehead and Woodruff²⁹⁶ describe three incorrect diagnoses of acute appendicitis, the lesion found being a solitary lymphoma of the appendix.

Delannoy and Verhaeghe²⁹⁷ report a case in which a 24 year old man was operated on after a diagnosis of acute appendicitis and found to have a single ulcer of the cecum, which was treated successfully by hemicolectomy performed on the right side.

289. Capone, A. J., and Miller, H.: Left-Sided Appendicitis in a Dextrocardiac Patient, *Am. J. Surg.* **71**:282-283, 1946.

290. Courty, M. A.: Pseudo-cancer recto-sigmoïdien du a une appendicite pelvienne, *Arch. d. mal. d. l'app. digestif* **35**:74-77, 1946.

291. Roque Suárez, A.: Diverticulosis apendicular, *Rev. Asoc. méd. argent.* **59**:775-779, 1945.

292. Bergeret, A., and Cotillon, J.: Les invaginations appendiculaires, *Arch. d. mal. de l'app. digestif* **35**:3-21, 1946.

293. Ingersoll, F. M., and Meigs, J. V.: Intussusception of the Vermiform Appendix, *Arch. Surg.* **51**:172-173 (Oct.) 1945.

294. White, W., and Ellis, R. C.: Polyps of the Appendix, *Am. J. Surg.* **70**:389-393, 1945.

295. Alecha, J. M., and Deluchi-Levene, A.: Cancer del apendice, *Rev. Asoc. méd. argent.* **60**:475-478, 1946.

296. Morehead, R. P., and Woodruff, W. E.: Solitary Giant Follicular Lymphoma of the Vermiform Appendix, *Arch. Path.* **40**:51-56 (July) 1945.

297. Delannoy, E., and Verhaeghe, M.: Ulcere simple du coeco-colon, hemi-colectomie droite guérison, *Arch. d. mal. de l'app. digestif* **34**:333-337, 1945.

PARASITIC AND DIARRHEAL DISEASES

Amebiasis.—Browne and McHardy²⁹⁸ ably review the recent literature of amebiasis. Manson-Bahr²⁹⁹ outlines the British conceptions of the disease. In active amebiasis ulcers are visible in the rectum in 80 per cent of the instances. In sigmoidoscopies on 258 patients amebic ulcers were demonstrated in 234; in 74 active amebas were found in the scrapings. In 26 this was the only way the diagnosis could be made. Of 535 cases encountered in twenty years, in only 1 was the disease fulminating and rapidly fatal. Acute fulminating conditions as encountered in Burma and India seldom occur in civilian practice. For the most part, amebiasis is a water-borne infection; it occurs in areas with poor sanitation and fertilization with human feces. In the United States the mean rate of infestation is reported at about 11.6 per cent; in Colombia (South America) it is 60 per cent, in China (Peiping) 20.3 per cent, in Java 23.6 per cent, in India (Madras) 21.9 per cent, in the Kola Peninsula (Arctic circle) 60.6 per cent and in English recruits 5.2 per cent. In Manson-Bahr's experience, emetine hydrochloride in courses at regular intervals and emetine bismuth iodide in doses of 2 to 3 grains (0.12 to 0.2 Gm.) for a total of 20 to 30 grains (1.29 to 1.94 Gm.) given in gelatin capsules or in sugar-coated form is usually successful in the eradication of the parasite and the relief of the symptoms. Daily rectal retention enemas of "quinoxyl" (chiniofon) in a 2.5 per cent solution and in amounts of 7 ounces (210 Gm.), to be retained six to eight hours for ten days, are of value. In 31 cases the relapse rate was 3.7 per cent in one year.

Neutral, cationic and anionic synthetic detergents were tested for cysticidal properties. Four of the cationic detergents were found to be efficient cysticides. The possible use of these substances for the sanitation of eating utensils, cleansing of shellfish, cleansing and disinfection of contaminated fruits and vegetables to be consumed raw and the cleansing of water mains is to be considered. The use of these substances in the disinfection of drinking water is still in the experimental stage.³⁰⁰

Druckmann and Schorr³⁰¹ studied the roentgenologic appearance of amebic colitis. The diffuse type is not characteristic and resembles that

298. Browne, D. C., and McHardy, G.: Review of Recent Literature on Amebiasis (1944-1945), *Gastroenterology* **6**:191-196, 1946.

299. Manson-Bahr, P.: British Conceptions of Amebiasis and Amebic Dysentery, *M. Rec.* **159**:213-216, 1946.

300. Fair, G. M.; Chang, S. L.; Taylor, M. P., and Wineman, M. A.: Destruction of Water Born Cysts of *Entamoeba Histolytica* by Synthetic Detergents, *Am. J. Pub. Health* **35**:228-232, 1945.

301. Druckmann, A., and Schorr, S.: The Roentgenological Manifestations of Amebiasis of the Large Intestine, *Am. J. Roentgenol.* **54**:145-148, 1945.

of idiopathic or ulcerative colitis. The localized type is denoted by the following signs: the relative length of the filling defect; the often multiple sites of constriction; the incompleteness of the narrowing of the lumen as compared with that in malignant stenosis; the insignificance or even absence of pain on distention by the barium enema in contrast with the acute pain of malignant stenosis; the gradual merging of the filling defect into the normal contours of the intestine; the partial maintenance of elasticity of the intestinal wall in amebiasis as evidenced by the widening of the lumen on introduction of barium; the more or less normal mucosal relief in the involved portion, and the more or less complete restoration to normal after vigorous antiamebic treatment.

In a group of 119 patients with suspected or proved amebiasis 67 were examined roentgenologically by Golden and Ducharme.³⁰² Deformity of the cecum was found in 30; of these, 21 had proved amebiasis, and in the other 9 the presence of the disease was not disproved. Of 53 patients with amebas in the stools, 33 had no abnormality of the cecum. Cecal deformity seemed more likely in patients with intestinal symptoms than in those without. Deformity was not found in two thirds of the patients with amebiasis. Cropper³⁰³ emphasizes the importance of proctosigmoidoscopy.

There are several instructive reports of amebiasis in the armed forces. Monthly examinations of purged stools of mess personnel in the Middle East by Tallant and Maisel³⁰⁴ revealed that 36.4 per cent acquired infection with *Endamoeba histolytica* during the two year period from November 1942 to November 1944. Ninety per cent of the native workmen examined had one or more pathogens in the feces; 22 per cent had *E. histolytica*. At the time of admission 26.5 per cent of 464 patients were asymptomatic; 35.7 per cent had mild symptoms, 24.4 per cent moderate symptoms and 13.4 per cent severe symptoms. No diarrhea occurred in 41.8 per cent. Loose stools were described in 38.8 per cent, and 24.4 per cent had severer diarrhea. Abdominal pain was present in 57.5 per cent, tenderness in 40.7 per cent, elevation of temperature in 15.6 per cent and leukocytosis in 11.9 per cent. Of the group with acute amebiasis, 18.1 per cent had a dysenteric stool, and of those with chronic amebiasis, 16.7 per cent. Sigmoidoscopically, 10.1 per cent of the patients with acute amebiasis, 10.2 per cent of those with chronic infection and 75 per cent of the carriers had a normal-appearing bowel wall.

302. Golden, R., and Ducharme, P.: The Clinical Significance of Deformity of the Cecum in Amebiasis, *Radiology* **45**:565-580, 1945.

303. Cropper, C. F. J.: La sigmoidoscopia en la disenteria amebiana, *Rev. Asoc. méd. argent.* **60**:450-453, 1946.

304. Tallant, E. J., and Maisel, A. L.: Amebiasis Among the American Armed Forces in the Middle East, *Arch. Int. Med.* **77**:597-613, (June) 1946.

Amebic involvement was found in 3.2 per cent of the appendectomies in the two year period.

Edson, Ingegno and D'Albora³⁰⁵ observed 39 cases in Northern Ireland. The clinical manifestations were mild; in the majority there was no blood, diarrhea or ulceration visible on proctoscopy, and motile amebas were not demonstrated in the stools or bowel scrapings. The source was not determined, but 26 of the patients were members of the same division. A survey of the stools of food handlers revealed that 20 per cent were cyst carriers. The soldiers had been on maneuvers in Tennessee and Louisiana. Of the group, 36 had diarrhea, 35 abdominal pain, 11 nausea, 10 audible peristalsis, 10 loss of weight, 9 bloody diarrhea, 8 vomiting, 7 fatigue, 5 constipation, 4 fever and 2 pain in the chest. Twenty-seven had short bouts of diarrhea characterized by four to eight watery or loose stools daily. The duration of symptoms was three months or less in 16, three to twelve months in 11 and more than one year in 12. In 4 of the 39 patients the characteristic ulcers were seen proctoscopically; in 3 others ulceration with generalized inflammation was noted. Examination of the stools revealed cysts in 26 of the group. In 13 others cysts or active amebas were found in proctoscopic specimens. Seven of the 39 were thought to have hepatitis. Response to carbarsone and chiniofon seemed good, but follow-up was not possible. In frank diarrhea and hepatitis emetine hydrochloride was used. Of 13 patients receiving emetine hydrochloride, electrocardiographic evidence of myocardial irritation was observed in 1.

In 1,000 consecutive unselected military returnees from overseas examined by Marion and Sweetsir³⁰⁶ *E. histolytica* was demonstrated in 168; 76.2 per cent were asymptomatic carriers, 20.2 per cent had chronic amebic dysentery and 3.6 per cent had acute amebic dysentery. The highest incidence was found in those who served in tropical areas overseas and in those who resided in the Southern states prior to enlistment in the army.

Ninety-five cases of amebiasis were found in a total population of 5,575 inmates and employees in a hospital for the insane. There were 10 deaths, all before the institution of a program of intensive treatment. Specimens of stools were obtained from 1,822 symptomless persons in the institution, of whom 1,184 were inmates and 638 employees. The incidence of amebiasis was 7.5 per cent in the inmates and 5.5 per cent in the employees. An average of 2.6 specimens were examined for each inmate and 3.2 specimens for each employee. Fourteen per cent of the

305. Edson, J. N.; Ingegno, A. P., and D'Albora, J. B.: Amebiasis: A Report of Thirty-Nine Cases Observed in an Army General Hospital Stationed in Northern Ireland, *Ann. Int. Med.* **23**:960-968, 1945.

306. Marion, D. F., and Sweetsir, F. N.: Amebiasis in Military Overseas Returnees, *Ann. Int. Med.* **24**:186-191, 1946.

374 inmates employed as food handlers and 6 per cent of the paid employees handling food were carriers.³⁰⁷

Two cases of amebic granuloma of the anal region are described by Howells.³⁰⁸ Both responded well to antiamebic treatment. Ameboma may occur years after the last recognized attack of dysentery.

Silverman and Leslie³⁰⁹ report 3 complicated, fatal cases of untreated ulceronecrotic amebic colitis with extensive and diffuse involvement of the colon. In 1 of them *Bacterium dysenteriae* (Duval) was also found in culture of the stools.

Hargreaves³¹⁰ considers emetine hydrochloride to be the most effective amebicidal drug even though it brings about recovery in only a small percentage of cases. The most efficient method of administration is to give 3 grains (0.2 Gm.) of emetine bismuth iodide nightly for ten days. The action of other drugs is discussed. Secondary bacterial infection is an important factor in severe refractory disease; in such cases administration of penicillin alone or succinylsulfathiazole and penicillin may bring about dramatic improvement and even be life saving.

An anhydrous form of lactic acid used by Sokoloff³¹¹ to treat 62 patients with acute and chronic types of infestation resulted in complete recovery in 54 per cent, no significant improvement in 19 per cent and considerable improvement in the remainder. Combined with iodine, this therapy was considered encouraging in its results.

Bruce³¹² used neoarsphenamine in the treatment of 15 patients with amebiasis. In 1 patient with severe dysentery there was a striking decrease in diarrhea, in 2 the diarrhea continued and in the majority the stools became sterile.

The use of neoarsphenamine was found to be effective, although because of the inconvenience of intravenous administration, it does not enjoy the popularity of other arsenicals given by mouth. Nevertheless, it is one more weapon available for those forms of amebiasis resistant to other methods of therapy.

Hawe³¹³ reviews in detail the surgical aspects of intestinal amebiasis. Perforation occurs in less than 3 per cent of the cases. The difficulty

307. Birnkrant, W. B.; Greenberg, M., and Most, H.: Amebiasis in a Hospital for the Insane, *Am. J. Pub. Health* **35**:805-814, 1945.

308. Howells, G.: Two Cases of Amoebic Granuloma, *Brit. M. J.* **2**:161-162, 1946.

309. Silverman, D. N., and Leslie, A.: Intractable Amebic Colitis with Special Reference to the Ulcero-Necrotic Form, *J. A. M. A.* **129**:187-190 (Sept. 15) 1945.

310. Hargreaves, W. H.: The Treatment of Amoebiasis with Special Reference to Chronic Amoebic Dysentery, *Quart. J. Med.* **15**:1-23, 1946.

311. Sokoloff, B.: A New Aspect in Treatment of Amebiasis, *Rev. Gastroenterol.* **12**:425-435, 1945.

312. Bruce, J. G.: The Use of Neoarsphenamine in the Treatment of Amebic Dysentery, *Ann. Int. Med.* **24**:1025-1028, 1946.

313. Hawe, P.: The Surgical Aspect of Intestinal Amebiasis, *Surg., Gynec. & Obst.* **81**:387-404, 1945.

in the differentiation of acute amebiasis and acute appendicitis is emphasized. Operation should not be advised in the presence of an inflammatory mass until the possibility of cecal amebiasis has been excluded. Appendectomy and cecostomy have no place in the treatment of this condition.

Schistosomiasis.—In keeping with the increased current interest in schistosomiasis japonica because of the exposure of Americans in the Orient, Faust, Wright, McMullen and Hunter³¹⁴ review the manifestations and diagnostic features in several hundred cases seen among military personnel in Leyte and among natives of all ages on Leyte, Mindanao and Samar, Philippine Islands.

There are three stages: the incubation period, the stage of acute symptoms and the stage of chronic symptoms. The disease begins with penetration of the skin by the fork-tailed larvae, the cercariae, released by the snail hosts in water. Within a few minutes a sharp needling pain may be noted at the site, followed in one to several days by an irritating, frequently unproductive bronchial cough or at times by a viscous discharge from the lungs. There may be no other distinct symptoms for two weeks or more during this prodromal period, then overnight moderate to severe urticaria develops. Anorexia, fatigability, malaise and loss of weight may then occur together with epigastric fulness, chilly sensations at night, night sweats and epigastric tenderness. Four or five weeks after exposure there may be profound anorexia, pain and fulness in the right side of the hypochondrium, general abdominal distress and painful diarrhea with blood-flecked feces. The patients were rarely seen until the disease was well advanced, and hence the prodromal stage was not well studied.

The acute stage, beginning when the mature, fertilized female worms lay their eggs which filter through the intestinal wall, usually to be evacuated in the stool in a few days, lasts three to four months, after which the early chronic stage begins. There are four varieties of the acute stage—fulminating, severe with sudden onset, insidious and asymptomatic.

Patients with the fulminating type of disease probably die frequently before a specific diagnosis is made. In the case reported the patient was seriously ill at the end of the incubation period, with acute systemic intoxication, a greatly enlarged, tender liver and abdominal distress. Although the stools were sterile, therapy with antimony and potassium tartrate, U. S. P., was begun. The patient died soon; necropsy revealed myriads of eggs in pseudoabscesses and pseudotubercles studding the surface and substance of the liver as well as other organs and tissues.

314. Faust, E. C.; Wright, W. H.; McMullen, D. B., and Hunter, G. W., III: The Diagnosis of Schistosomiasis Japonica: I. The Symptoms, Signs and Physical Findings Characteristic of Schistosomiasis Japonica at Different Stages in the Development of the Disease, *Am. J. Trop. Med.* **26**:87-110, 1946.

Numerous cases in which the disease was in the "severe, with sudden onset" category were studied. The median date of initial symptoms was four to five weeks following exposure. The earliest entries in the records of the hospital were: fever of unexplained origin, urticaria, angioneurotic edema, gastrointestinal distress, acute diarrhea, dengue, suspected infectious hepatitis and infection of the upper respiratory tract. There were varying degrees of eosinophilia; in 77 per cent of the patients in one group the eosinophil content was 30 per cent or more, in 1 patient it was over 90 per cent, and in only 6 per cent was it less than 10 per cent. After four or five months several patients treated with faudin (40 to 80 cc.) were still sick and apathetic, with distressed hepatic facies. In many of these proctoscopy revealed slightly elevated yellowish papillae, 1 to 3 mm. in diameter, from a few centimeters above the junction of the sigmoid and rectum to a few centimeters below this level.

In the insidious type the symptoms and signs are minimal; diagnosis is made only after eggs are found in the stools.

The asymptomatic patients belong to the category of carriers.

Recovery of the eggs constitutes the only method of specific diagnosis. While this is relatively easy in the acute stage, it becomes increasingly difficult in the chronic stage.

Hunt's³¹⁵ observations are similar.

Alves and Blair³¹⁶ report the results in 100 cases of the two day treatment with sodium antimonyl tartrate in doses of 12 mg. per kilogram of body weight, with a multiple syringe technic of four daily intravenous injections. Each patient received six injections in all. No viable eggs were found in any case immediately after treatment or two or three months later. In 53 cases followed for two months the reaction to the skin test with cercarial antigen became negative in 73 per cent. Nine of the 14 cases in which the reaction to the skin test was positive were observed for three months; the reaction became negative in 6. The method is suggested for mass treatment in the control of schistosomiasis.

Hookworm.—Hesselbrock and others³¹⁷ carried out extensive examinations for parasites, using various technics in 14,250 stools from 2,464 patients, most of them returned from various areas overseas. The results depended to a considerable extent on the endemic infections in these areas. The commonest parasites were hookworm and whipworm.

315. Hunt, A. R.: Schistosomiasis in Naval Personnel, U. S. Nav. M. Bull. 45:407-419, 1945.

316. Alves, W., and Blair, D. M.: Schistosomiasis: Intensive Treatment with Antimony, Lancet 1:9-12, 1946.

317. Hesselbrock, W. B.; Lippincott, S. W., and Palmer, E. D.: Large-Scale Routine Examinations of Stool for Parasites: Practical Experience in a General Hospital in the Zone of the Interior, Am. J. Clin. Path. 16:264-269, 1946.

Page,³¹⁸ in a study of 1,353 men in a hospital for the treatment of gastrointestinal diseases, found the presence of eosinophilia of no particular diagnostic value except in intestinal parasitic diseases, especially hookworm.

Hodes and Keefer,³¹⁹ in a study of 125 soldiers with proved ankylostomiasis, found roentgenologic abnormalities in the small intestine in approximately 60 per cent. The alterations consisted in excessive peristalsis and segmental contractions, with distortion of the mucosal pattern.

Giardia Lamblia.—Twenty-one cases of diarrhea attributed to infestation with *Giardia lamblia* are described by Fraser and Taylor.³²⁰ "Acranil" (3-chloro-7-methoxy-9-[2-hydroxy-3-diethylamino]-propyl-aminoacridine dehydrochloride), an acridine derivative closely related to quinacrine hydrochloride, was found by Berberian³²¹ to be a highly efficient chemotherapeutic agent in tests on 50 cases of infection with *G. lamblia* in children, as shown by the negative reactions in five consecutive weekly examinations of stools. The drug was well tolerated. No parasitocidal effect was observed on concomitant protozoal infections with *E. histolytica*, *E. coli*, *Iodamoeba williamsi*, *Endolimax nana* and *Chilomastix mesnili* or on nematode infestations with *Ascaris lumbricoides*, *Trichuris trichiura* and *Enterobius vermicularis*. Some therapeutic effect was noted against cestode infestations with *Hymenolepis nana* and *Taenia saginata*.

Tapeworm.—A practical method is described for the detection of *Diphyllobothrium latum* rapidly in specimens with few ova by the utilization of polarized light; the external membrane of these ova are double-refracting.³²²

Beetle Larvae.—Accidental parasitism by coleopteran (beetle) larvae in an 8 month old white boy is reported by Palmer.³²³ At the age of 5 months the infant passed by rectum a white worm about an inch (2.54 cm.) long. Several similar worms were expelled in the next three months. Adult beetles were found in a box of precooked cereal; the

318. Page, R. C.: Eosinophilia on a Gastro-Intestinal Hospital Service: Case Reports on Four Patients with a Syndrome of Eosinophilia, Leucocytosis and Gastro-Intestinal Complaints, *Gastroenterology* 5:373-386, 1945.

319. Hodes, P. J., and Keefer, G. P.: Hookworm Disease: A Small Intestinal Study, *Am. J. Roentgenol.* 54:728-742, 1945.

320. Fraser, J. F., and Taylor, R.: Diarrhea Due to *Giardia Lamblia*, *Brit. M. J.* 2:184-185, 1945.

321. Berberian, D. A.: Treatment of Lamblasis with Acranil, *Am. J. Trop. Med.* 25:441-444, 1945.

322. Bohrod, M. G.: Detection of *Diphyllobothrium Latum* Ova in Polarized Light, *Am. J. Clin. Path. (Tech. Sect.)* 15:77-78, 1945.

323. Palmer, E. D.: Intestinal Canthariasis Due to *Tenebrio Molitor*, *J. Parasitol.* 32:54-55, 1945.

eggs are thought to have been ingested with the feedings. Purges and enemas were ineffective.

Myiasis.—Of 60 volunteers fed with living maggots of *Musca domestica*, *Calliphora* and *Sarcophaga* by Kenney³²⁴ under conditions to avoid their destruction in the stomach, symptoms of gastrointestinal disturbance—nausea, vomiting, intestinal cramps and diarrhea—developed in 50. All symptoms disappeared within forty-eight hours following the elimination of larvae in the vomitus and stools; only a few of the larvae were found alive. These investigations seem to indicate that while temporary disturbance may follow the ingestion of such dipterous larvae they do not produce a true intestinal myiasis in human beings.

Spirochetes in Feces.—Dark field examinations of feces of 199 persons in North Africa disclosed the presence of spirochetes of the *Borrelia* type in about one fourth. A low fat diet did not influence the frequency of the occurrence. Spirochetes form a part of the normal flora of the feces of mice and guinea pigs as well as of human beings.³²⁵

Steatorrhea and Sprue.—Cooke and others³²⁶ carried out studies on fat balance in 120 patients. Of these, 29 had idiopathic steatorrhea, 21 had tropical sprue, 7 had pancreatitis, 6 had surgical conditions (as gastocolic fistulas), 6 had malnutrition, 2 had lymphatic obstruction and in 8 the conditions were classified as miscellaneous. Of 41 control patients, 15 had diarrhea, 12 had anemia and the conditions in 14 were classified as miscellaneous. The objective is the better understanding of the mechanisms of absorption of fat in health and in disease. To date the work has consisted in an evaluation of methods and the development of criteria for the assessment of abnormality, a diet containing 50 Gm. of fat being used.

The gross and microscopic examination of the feces for fat is unreliable. The percentage of fat in dried feces is not accurate in the differentiation of normal from abnormal absorption. The percentage of hydrolysis of fecal fat is considered insignificant because of evidence that absorption of fat is not dependent on splitting of neutral fat (Frazer, Schulman and Stewart, 1944). The former notion that fat hydrolysis is an index of pancreatic function is rejected because of the presence of lipase elsewhere in the gastrointestinal tract. Intestinal hurry is not considered a cause of malabsorption.

324. Kenney, M.: Experimental Intestinal Myiasis in Man, *Proc. Soc. Exper. Biol. & Med.* **60**:235-237, 1945.

325. Gowen, G. H.: Spirochaetes in Feces, *Illinois M. J.* **88**:202-203, 1945.

326. Cooke, W. T.; Elkes, J. J.; Frazer, A. C.; Parkes, J.; Peeney, A. L. P.; Sammons, H. G., and Thomas, G.: Anomalies of Intestinal Absorption of Fat: I. The Determination and Significance of Faecal Fat, *Quart. J. Med.* **15**:141-155, 1946.

It is concluded that the only reliable method for the detection of defects in absorption of fat is the fat balance technic, in which is utilized the Cammidge modifications of the Schmidt-Werner method, or a wet extraction method. By correlation of the intake and output of fat the percentage of absorption is calculated.

In the 41 control patients more than 95 per cent of the dietary fat was absorbed, the variations ranging between 91 and 99 per cent; the average total fat content in the stool was 16.37 per cent and the average fatty acid fraction 4.5 per cent. In the 29 cases of idiopathic steatorrhea the average absorption was 73 per cent, the average total fat content in the stool 35.1 per cent and the average fatty acid fraction 15.5 per cent.

Black, Fourman and Trinder³²⁷ discuss, in a preliminary communication, the results of experiments on fat balance in early cases of sprue. The percentage of absorption of fat was obtained by the formula:

$$\frac{(\text{Dietary fat minus excreted fat}) \times 100}{\text{dietary fat}}$$

The studies led to the conclusion that a moderate increase in dietary fat is not necessarily attended by a lowering of the percentage of fat absorption. Variations are minimal. The relative constancy of the percentage of fat absorption is considered evidence opposing the theories that sprue is caused by diminished motility of the villi or reduction in absorptive surface. The constancy of the percentage of fat absorption with differing intakes is more easily explained by theories based on the failure of an enzyme system such as that concerned in phosphorylation (Stannus, 1942). The results confirm those of earlier studies by demonstration of the fact that even in moderately severe sprue 60 to 80 per cent of the ingested fat is absorbed. In the earlier phases of sprue there is satisfactory absorption of glucose, iron, sodium, chloride and nitrogen, but subsequently the defect in absorption includes these substances.

The therapeutic studies are of interest. Liver extract did not have a rapid effect on absorption of fat; yeast extract was more effective. It is pointed out, however, that Barker and Rhoads (1937) had better results with larger doses of crude liver extract. The authors draw the general conclusion that there is a factor in yeast extract, probably present also in crude liver extract in lesser amounts, which improves absorption of fat in patients with sprue; it is not nicotinic acid, riboflavin or pantothenic acid but may be similar to Castle's extrinsic factor. The authors point out that the active factor in the yeast extract may have been folic acid.

327. Black, D. A. K.; Fourman, L. P. R., and Trinder, P.: Fat Absorption in Tropical Sprue, *Lancet* 1:574-575, 1946.

Cayer, Ruffin and Perlzweig³²⁸ report studies of vitamin levels in (a) 12 cases in which a diagnosis of sprue was made carefully on a basis of the presence of steatorrhea, glossitis, macrocytic hyperchromic anemia, a flat glucose tolerance curve and notable loss of weight; (b) 30 cases in which the condition was diagnosed clinically as mild or early vitamin B deficiency and (c) a control group of 30 normal medical students. The conclusions were: 1. Multiple deficiencies of vitamin B complex are the rule in patients with sprue. 2. The plasma levels of vitamin A and carotene in patients with sprue are significantly lower than the levels in normal persons or in those with clinical evidence of B complex deficiency. 3. The determination of plasma levels of vitamin A and carotene is a useful laboratory procedure in the diagnosis of sprue.

In 3 cases of sprue 15 mg. of synthetic L. casei factor was administered intramuscularly, with significant improvement, by Darby, Jones and Johnson.³²⁹ Glossitis disappeared in three or four days, diarrhea subsided and reticulocyte responses of 15.3 and 43 per cent occurred in the first 2 cases on the eighth and sixth days of treatment.

Spies and others³³⁰ treated 4 patients with tropical sprue with 5-methyl uracil (thymine) and observed a definite hematologic response after the daily ingestion of 15 Gm. of the drug. Reticulocytosis began on the fourth or fifth day, reaching its peak on the eighth or ninth day and followed by an increase in erythrocytes and the hemoglobin content. Clinical improvement was indicated by an increase in appetite and strength, a disappearance of glossitis and of burning and soreness of the tongue and a return of the stools to normal as early as the fourth day. Apparently the hematologic response evoked by synthetic 5-methyl uracil in the macrocytic anemia of tropical sprue parallels that which follows the administration of synthetic folic acid. The clinical response, however, with this dosage is less dramatic than that observed with folic acid.

An observation made by Carruthers³³¹ may be of considerable clinical significance. In 6 cases of chronic diarrhea of varied causation folic acid therapy restored the stools to normal in two to five days. It may well be that many instances of chronic mild diarrhea are manifestations of steatorrhea or of the sprue syndrome, curable by administration of folic acid. There is no pathognomonic sign or symptom of sprue; aside

328. Cayer, D.; Ruffin, J. M., and Perlzweig, W. A.: Vitamin Levels in Sprue, *Am. J. M. Sc.* **210**:200-207, 1945.

329. Darby, W. J.; Jones, E., and Johnson, H. C.: The Use of Synthetic L. Casei Factor in the Treatment of Sprue, *Science* **103**:108, 1946.

330. Spies, T. D.; Frommeyer, W. B.; Garcia Lopez, G.; Lopez Toca, R., and Gwinner, G.: Haemopoietic Action of 5-Methyl Uracil (Thymine) in Tropical Sprue, *Lancet* **1**:883-885, 1946.

331. Carruthers, L. B.: Chronic Diarrhea Treated with Folic Acid, *Lancet* **1**:849-850, 1946.

from the use of folic acid, which has yet to stand the test of time, and despite the recognized value of liver extract, it still may be said that there is no specific treatment or known cause for this fascinating disease. The clinical forms and manifestations may be even more varied and bizarre than now recognized.

In a study of 23 cases of pellagra in non-European children in Johannesburg the main clinical findings were edema, dermatitis, cheilosis, graying of the hair with degrees of alopecia, steatorrhea and a large fatty liver. Powdered stomach, given orally, was found to have a lipotropic action in infantile pellagra. In view of the low fat content of the diet, the steatorrhea was thought to be due to an increased endogenous excretion of fat into the bowel rather than to malabsorption of dietary fat. The authors suggest the use of powdered stomach in other diseases in which steatorrhea is a prominent feature.³³²

Simulating sprue, but of known causation, are the steatorrheas produced by lymphatic obstruction, such as those produced in the 3 cases reported by Pearson, due to tuberculosis, nonspecific inflammation and a reticulum cell sarcoma respectively.³³³ In the case of intestinal lipodystrophy (Whipple's disease) described by Fitzgerald and Kinney³³⁴ the bizarre hematologic picture caused it to be confused with lymphatic leukemia and hemolytic icterus. In the case analyzed by Amsterdam and Grayzel³³⁵ the classical symptoms were present. Necropsy revealed mesenteric lymphadenopathy with lipid replacement of the lymph nodes and enlarged intestinal villi with the characteristic fat-laden cells in the mucosa and submucosa.

Infantile Diarrhea.—Sterility of supplies, limitation of outside contacts and the realization that all children in the nursery are potential sources of infection regardless of the state of their health aid in limiting diarrheal disease, according to Watts.³³⁶

Rapoport and Dodd³³⁷ describe 7 cases of hypoprothrombinemia, usually accompanied with bleeding, in infants suffering from chronic

332. Gillman, T., and Gillman, J.: Powdered Stomach in Treatment of Fatty Liver and Other Manifestations of Infantile Pellagra: Its Significance with Reference to the Problems of Edema and Steatorrhea in Infants and in Adults, *Arch. Int. Med.* **76**:63-74 (Aug.) 1945.

333. Pearson, R. S. B.: Steatorrhea Due to Lymphatic Obstruction, *Proc. Roy. Soc. Med.* **38**:385-387, 1945.

334. Fitzgerald, P. J., and Kinney, T. D.: Intestinal Lipodystrophy (Whipple's Disease), *Am. J. Path.* **21**:1069-1089, 1945.

335. Amsterdam, H. J., and Grayzel, D. M.: Intestinal Lipodystrophy (Lipophagia Granulomatosis or Whipple's Disease), *Am. J. M. Sc.* **210**:605-611, 1945.

336. Watts, J.: Practical Implications of the Epidemiology of the Diarrheal Diseases of the Newborn, *Am. J. Pub. Health* **35**:1205-1209, 1945.

337. Rapoport, S., and Dodd, K.: Hypoprothrombinemia in Infants with Diarrhea, *Am. J. Dis. Child.* **71**:611-617 (June) 1946.

diarrhea. In 6 there was no bleeding after administration of vitamin K; in 5 the prothrombin time returned promptly to normal. The prophylactic use of vitamin K is suggested in instances of prolonged malnutrition in infancy and childhood.

Epidemic Diarrhea.—Brown and others³³⁸ report an outbreak of epidemic diarrhea and vomiting of unknown origin, suggesting a virus infection.

Diabetic Diarrhea.—Sheridan and Bailey³³⁹ describe intermittent nocturnal diarrhea as a distinct syndrome in patients with diabetes mellitus. Intermittent diarrhea occurred in 34 of 40 cases and nocturnal incontinence in 31. Diabetic neuritis preceded the onset of the diarrhea in 58 per cent. The authors suggest that the diarrhea may be a manifestation of diabetic neuropathy. Crude liver extract administered parenterally is said to offer the most effective symptomatic treatment.

Bacillary Dysentery.—Kokko³⁴⁰ gives a complete and detailed analysis of an extensive epidemic of bacillary dysentery (Flexner's). Cultures which were positive for the organism were obtained in 32 per cent of the cases examined. Flexner's bacilli were isolated from 58 per cent of samples of the excrement taken in the first five days of the illness. Cultures of the organism were oftener obtained with samples of feces preserved in a 30 per cent solution of glycerin and 0.6 per cent solution of sodium chloride in water than with those sent in for examination without the preservative. The bacillus was never found in samples of blood, urine, synovial fluid or gastric contents. It remained alive in excrements for at least two days generally and in most cases for a minimum of three days. It was preserved better by cold than by heat.

The biochemical activity of the different strains varied in ability to ferment arabinose, maltose, saccharose, raffinose, dextrin and sorbite and to produce indole. This variation was shown not only between different strains but also between the subcultures from different colonies of one single strain and subsequent cultures at different times. More than 15 per cent of the examined strains decomposed both maltose and saccharose, producing acid, a peculiarity not compatible with the three principal types of known Flexner groups. Kokko continues with an exhaustive discussion of the biochemical and serologic typing of Flexner organisms, too technical to summarize here.

338. Brown, G.; Crawford, G. J., and Stent, L.: Outbreak of Epidemic Diarrhea and Vomiting in a General Hospital and Surrounding District, *Brit. M. J.* **2**:524-526, 1945.

339. Sheridan, E. P.; and Bailey, C. C.: Diabetic Nocturnal Diarrhea, *J. A. M. A.* **130**:632-634 (March 9) 1946.

340. Kokko, U. P.: Flexner Bacilli and Flexner Dysentery, *Acta med. Scandinav.*, 1945, supp. 167, pp. 1-203.

Of clinical interest is the observation that the organisms disappeared from the feces of more than 90 per cent of the patients before clinical recovery had taken place; the longest time of excretion after clinical recovery was four weeks. The greatest role in the spread of the disease was played by those who were only slightly ill or who were not taken into the hospital immediately after falling ill. Attempts to cultivate Flexner's bacilli from eighty-eight samples of flies (*Stomoxys calcitrans*) caught in different places in the region of the epidemic were unsuccessful.

Most of the sick, 65 to 75 per cent, were so slightly ill that they did not require treatment by a physician. The illness commenced in general with high fever and diarrhea without any prodromal signs. The other symptoms were: sharp pains in the stomach, headache, vomiting, vertigo, pains in the limbs and joints and general indisposition. The most characteristic symptoms were violent diarrhea and slimy, bloody feces (87 per cent). More than 40 per cent of the patients vomited. Fever occurred in 95 per cent of the patients; in more than 40 per cent the temperature rose to more than 39 C. (102.2 F.). Usually the fever lasted two days only. A great many nervous symptoms suggestive of increased cerebral pressure appeared in patients with the most serious attacks.

The commonest complications were pains of rheumatic nature in the muscles and joints, arthritis in the big joints, mostly the knees, pains in the eyes, conjunctivitis and pains when urinating, with occasional purulent urethritis (Reiter's syndrome). There were only 4 cases of peritonitis.

In two thirds of the patients the illness lasted not more than fifteen days. Relapses occurred in 4.5 per cent, about 40 per cent of this number being without fever. A rather general occurrence was lassitude that appeared ten or twenty days after recovery and lasted for a period of from several days to a couple of weeks.

The death rate among patients treated by a physician was 2 per million, 70 per cent of the deaths occurring in the first two weeks and being due to circulatory failure, increased cerebral pressure or complicating diseases.

Further studies of the complicated problem of the morphologic, biochemical and serologic classification of the *Salmonella* organisms are contained in the papers of Felsenfeld,³⁴¹ Thomas and Levine,³⁴² Nelson, Tenbroeck and Dammin³⁴³ and Thompson, White and Schafer.³⁴⁴

341. Felsenfeld, O.: The *Salmonella* Problem, *Am. J. Clin. Path.* **15**:584-608, 1945.

342. Thomas, A. R., Jr., and Levine, M.: The Serum Agglutination Reaction in Diagnosis of Bacillary Dysentery, *Am. J. Clin. Path.* **16**:98-110, 1946.

343. Nelson, J. B.; Tenbroeck, C., and Dammin, G. J.: Distribution of *Shigella* in India as Determined by Spot Agglutination with Absorbed Sera, *Am. J. Pub. Health* **35**:1282-1286, 1945.

Ferris, Hertzberg and Atkinson³⁴⁵ describe another new strain isolated from 26 to 29 patients. We wonder if the endless typing and subtyping of *Salmonella* organisms is of practical value or of real fundamental importance; a new bacteriologic concept and a new approach to the problem seem needed.

In a survey by Slesinger and Elrod³⁴⁶ of 264 German prisoners of war, *Shigella* grew in the cultures of 24.6 per cent; parasites and ova were present in 16 per cent, for *Escherichia coli* and ova of *Ascaris lumbricoides* being the most frequent.

The initial enthusiasm for sulfonamide drugs in the treatment of enteric infections is now beginning to subside, although some authors still report definite benefit from their use. Thus, Moore and his associates,³⁴⁷ on the basis of relative in vitro activity, fecal concentration of free sulfonamide compounds and risk of toxicity from systemic absorption, list drugs in the following order of preference for the treatment of bacillary dysentery: enteric-coated sulfadiazine, similarly coated sulfathiazole, succinylsulfathiazole, uncoated sulfadiazine, uncoated sulfathiazole and sulfaguanidine. White and others³⁴⁸ found sulfacarboxythiazole (2-sulfanilamido-5-carboxythiazole) about as active as sulfaguanidine against twelve dysentery strains in vitro and against coliform bacilli in mice. With respect to solubility, absorption and mode of action, sulfacarboxythiazole appeared to be similar to phthalysulfathiazole. Sulfathiadiazole (2-sulfanilamido-1, 3, 4-thiadiazole), when compared with sulfaguanidine, was found to be about ten times as soluble at pH 6.5, from four to eight times as active against dysentery strains in vitro and more active against coliform bacteria in mice. In 87 cases Smith³⁴⁹ found that the most effective period for treatment is during the first twenty-four hours. Early treatment with sulfadiazine usually led to prompt cessation of diarrhea and cramps. The healing of mucosal lesions lagged behind the symptomatic relief.

344. Thompson, C. M.; White, B. V., and Schafer, W. L.: *Shigellosis Studies: Etiology and Clinical Features*, U. S. Nav. M. Bull. **46**:528-540, 1946.

345. Ferris, A. A.; Hertzberg, R., and Atkinson, H.: *An Epidemic of Diarrhea Caused by a New Strain of the Salmonella Group*, M. J. Australia **2**:368-371, 1945.

346. Slesinger, H. A., and Elrod, R. P.: *Survey of Dysentery in Prisoners of War*, Ann. Int. Med. **24**:1014-1024, 1946.

347. Moore, F. J.; Kessel, J. F.; Simonsen, D. G., and Marmorston, J.: *Experimental Basis of Sulfonamide Therapy in Bacillary Dysentery*, J. Infect. Dis. **78**:25-31, 1946.

348. White, H. J.; Bell, P. H.; Bone, J. F.; Dempsey, J. C., and Lee, M. E.: *Sulfonamides for Bacillary Dysentery*, J. Pharmacol. & Exper. Therap. **85**:247-257, 1945.

349. Smith, L. A.: *Shiga Dysentery*, J. A. M. A. **130**:18-22 (Jan. 5) 1946.

Vollum and Wylie³⁵⁰ describe results of an outbreak of Sonne dysentery in two schools in the same building. All the boys in one school were treated with succinylsulfathiazole, 6 Gm. a day, the members of the other school being used as controls. In the control group 11 of 33 continued to excrete the organism. In the treated group cultures from all 37 boys became negative for the organism except a single swab from 1 boy which was positive three weeks after therapy.

More equivocal is the investigation of bacillary dysentery in acutely ill and carrier monkeys (*Macaca mulatta*) and of the therapeutic value of sulfaguanidine in these infections reported by Hoskins and Dack.³⁵¹ Two established carriers of *Bacterium dysenteriae* (Flexner's) treated with sulfaguanidine before the development of symptoms failed to be cleared of the organism by the drug. Among 10 monkeys ill with acute dysentery, 5 improved with sulfaguanidine therapy and 5 were not improved. One of the improved animals became a convalescent carrier. The organism recovered by Cheever³⁵² in an epidemic involving 6,000 sailors in July and August, 1945, was relatively resistant to sulfadiazine and sulfathiazole. White and his associates³⁵³ found that sulfadiazine given in standard dosage was not effective in an outbreak involving 35 cases. In a later report of 1,300 cases the organism was described as resistant to sulfonamide drugs.³⁵⁴ Brodie and others³⁵⁵ treated 88 patients with bacillary dysentery with phthalylsulfathiazole. The incidence of relapse was high, involving 45 of the 88 patients. Of the patients studied bacteriologically, 28 per cent of those relapsing yielded a positive culture during convalescence, compared with .13 per cent of those not relapsing.

In a study by Elsom, Pepper and Forrester³⁵⁶ of 334 cases of bacillary dysentery in Chinese soldiers in an army general hospital in India, one

350. Vollum, R. L., and Wylie, J. A. H.: Control of Sonne Dysentery with Succinylsulphathiazole, *Lancet* **1**:91-92, 1946.

351. Hoskins, D., and Dack, G. M.: A Study of Chemotherapy in Experimental Bacillary Dysentery of *Macaca Mulatta* with Emphasis on Clearing of the Carrier State, *J. Infect. Dis.* **78**:32-39, 1946.

352. Cheever, F. S.: Dysentery Outbreak Aboard Naval Vessels in San Pedro Bay, Phillipine Islands, *U. S. Nav. M. Bull.* **46**:479-494, 1946.

353. White, B. V.; Thompson, C. M.; Schafer, W. L., and Jacobson, M. A.: Shigellosis Studies: Resistance of *Shigella Flexner* III to Therapy with Sulfadiazine, *U. S. Nav. M. Bull.* **46**:704-708, 1946.

354. Thompson, C. M., and White, B. V.: Shigellosis Studies: Clinical Observations on Dysentery Caused by *Shigella Flexner* III, *U. S. Nav. M. Bull.* **46**:901-910, 1946.

355. Brodie, J.; Cook, R. P.; Drysdale, C. F., and McIntosh, D. G.: Treatment of Sonne III Bacillary Dysentery and Bacillary Dysentery ("Clinical") with Phthalyl Sulphathiazole, *Brit. M. J.* **1**:948-950, 1946.

356. Elsom, K. A.; Pepper, D. S., and Forrester, J. S.: The Treatment of Bacillary Dysentery in Chinese Soldiers with Sulfaguanidine and Sulfadiazine, *Am. J. M. Sc.* **211**:103-109, 1946.

third were treated with sulfaguanidine, one third with sulfadiazine and one third with placebos. Neither of the sulfonamide drugs shortened the course of the disease, ameliorated the symptoms or altered the eventual outcome.

After an epidemic of bacillary dysentery, Getty and his co-workers³⁵⁷ cultured the stools of the men in an entire division; 327 carriers were isolated. Fifty-five were treated with 29 Gm. each of sulfathiazole, 221 with 73.5 Gm. of sulfaguanidine and 51 with 29 Gm. of sulfadiazine. No significant difference in the eradication of the carrier state was noted with the sulfonamide compounds in the dosages used.

On the basis of experimental laboratory data, sulfathiazole and sulfadiazine were used by Jones and Lee³⁵⁸ during a small epidemic among children, but no well defined effects were observed. In general, the available antibiotics were not effective.

The contradictory evidence is impressive. Bacillary dysentery is a self-limited disease of variable severity and duration. Can it be that the original observers did not bear this in mind sufficiently and were misled in their interpretation of "good results"? Are the differences in sensitivity to sulfonamide compounds sufficient to account for the conflicting reports? these questions need further elucidation.

Morrison³⁵⁹ found "good results" in the treatment of 100 patients with different types of diarrhea with tomato pomace.

Olitzki and Bichowsky³⁶⁰ report that small quantities of toxoid, prepared from cultures of *Shigella dysenteriae*, absorbed on alum and concentrated and injected subcutaneously immunized rabbits against multiple lethal doses of dysentery toxin.

Typhoid.—Morgan³⁶¹ finds that purified antigens of *Eberthella typhosa*, *Salmonella paratyphi* and *S. schottmulleri* produced less local and constitutional reaction than a triple bacterial vaccine when injected subcutaneously in man. These purified antigens possess the advantages of potency, stability and compactness.

357. Getty, R. W.; Clifton, F.; Harings, R.; Rukes, J. M., and Rosch, S.: Treatment of Bacillary Dysentery Carriers with Sulfonamides, U. S. Nav. M. Bull. **45**:914-918, 1945.

358. Jones, J. A., and Lee, H. F.: *Salmonella Suipestifer* Infection in Children: A Report of Eighteen Cases, Am. J. M. Sc. **211**:723-728, 1946.

359. Morrison, L. M.: The Control of Diarrhea by Tomato Pomace, Am. J. Digest. Dis. **13**:196-198, 1946.

360. Olitzki, L., and Bichowsky, L.: The Preparation of a Potent Toxin of *Shigella Dysenteriae* (Shiga) on a Semi Synthetic Medium and Its Use in the Preparation of an Alum Precipitated Toxoid, J. Immunol. **52**:293-300, 1946.

361. Morgan, H. R.: Active Immunization with Purified Somatic Antigens of *Eberthella Typhosa*, *Salmonella Paratyphi* and *Salmonella Schottmulleri*, Am. J. Pub. Health **35**:614-620, 1945.

In a group of 360 young women Duncan and his associates³⁶² noted 18 cases of typhoid in epidemic form, with 1 death. A food handler whose stools contained *E. typhosa* had prepared orange juice for the group.

Bigger³⁶³ finds that the combination of penicillin and sulfathiazole has a pronounced bactericidal effect on *Bact. typhosum* in vitro and suggests its use clinically, both agents to be given in full doses for five to seven days and then the use of both discontinued. The dosage of penicillin should be adequate to maintain a concentration of over 2 units a day. If evidence of the continued presence of typhoid bacilli persists, therapy should be resumed and continued for a further four days.

Cholera.—Three hundred and seventy-two cases of clinical cholera were studied by Amberson.³⁶⁴ In 60 controls the mortality was 38.3 per cent, in 35 patients treated with plasma and chemotherapy there were no deaths and in 277 treated with chemotherapy alone the mortality was 1.1 per cent. Of 78 patients admitted in frank shock or collapse, in 35 treated with plasma plus chemotherapy there was no mortality, in 19 treated with chemotherapy alone the mortality was 15.8 per cent and in 24 untreated patients it was 95.8 per cent.

Vibrio Jejuni.—In outbreaks of gastroenteritis occurring simultaneously in two adjacent institutions epidemiologic studies pointed toward milk as the vehicle for the infective agent.³⁶⁵ *Spirillum* was found in 13 of 39 cultures of the blood taken during chills and in the feces of 31 of 73 patients. This vibrio, S20, may be identified with *Vibrio jejuni* described by Jones and Little (1931) and Smith and Orsutt (1927), apparently inducing diarrhea and enteritis in cattle.

Chronic Nonspecific Ulcerative Colitis.—Ivy and Clarke³⁶⁶ drained the bile and pancreatic juice directly into the appendix and colon in 6 dogs; no pathologic changes were noted in the colonic mucosa for periods varying from six to twenty-three weeks.

In nine years two carcinomas of the colon complicating chronic ulcerative colitis were observed by Renshaw and Brownell,³⁶⁷ an incidence

362. Duncan, T. G.; Doull, J. A.; Miller, E. R., and Bancroft, H.: Outbreak of Typhoid Fever with Orange Juice as the Vehicle Illustrating the Value of Immunization, *Am. J. Pub. Health* **36**:34-36, 1946.

363. Bigger, J. W.: Synergic Action of Penicillin and Sulphathiazole on *Bacterium Typhosum*, *Lancet* **1**:81-83, 1946.

364. Amberson, J. M.: Report on Cholera Studies in Calcutta, *U. S. Nav. M. Bull.* **45**:1049-1053, 1945.

365. Levy, A. J.: A Gastro-Enteritis Outbreak Probably Due to a Bovine Strain of *Vibrio*, *Yale J. Biol. & Med.* **18**:243-258, 1946.

366. Ivy, J. H., and Clarke, B. G.: Is Bile and Pancreatic Juice a Factor in the Genesis of Ulcerative Colitis? An Experimental Study, *Gastroenterology* **5**:416-417, 1945.

367. Renshaw, R. J. F., and Brownell, T. S.: Carcinoma Complicating Ulcerative Colitis, *Cleveland Clin. Quart.* **12**:123-127, 1945.

of 0.59 per cent of all cases of chronic ulcerative colitis and 1.5 per cent of cases in which the condition occurred in patients under 30 years of age. Johnson³⁶⁸ gives an excellent discussion of the diagnosis and management of the disease.

Barbosa, Bargaen and Dixon,³⁶⁹ in a most instructive paper on regional segmental colitis, state that in a twenty year period from 1923 to 1943 140 (4 per cent) of 4,000 cases of the disease were classified as regional. The right colon was more frequently involved than the left and the ascending portion less frequently than the transverse. In 25 (18 per cent) the terminal part of the ileum was diseased. While the histologic appearance of colitis and regional enteritis may be similar, the primary infection may be different. There is no typical clinical course; the diarrhea is rarely severe. Loss of weight is common, fever inconstant and anemia not infrequent; the sedimentation rate parallels the degree of activity of the disease process. Secondary polypoid hyperplasia, rarely neoplastic, is observed. Obstructing stricture is uncommon and rectal complications as well as perirectal abscess, anal fistula and suppurative condylomas are frequent. The proctoscopic examination may reveal a normal rectum. Systemic complications are infrequent.

In a detailed study of the effect of sulfonamide drugs, no definite conclusions were reached. The evidence seemed to indicate that in acute episodes one of the sulfonamide compounds should be given; succinylsulfathiazole is the preparation of choice. In a group of 58 patients treated with these drugs the disease recurred in 53 per cent in one year; of 29 patients not given sulfonamide drugs it recurred in 28 per cent. Of 39 patients followed two years and treated with sulfonamide drugs, 62 per cent reported recurrence; of 24 not given the drugs, 33 per cent reported recurrence. Of the 28 treated surgically, the disease recurred in 25 per cent. Of 24 followed two to three years with sulfonamide therapy, the disease recurred in 58 per cent, and of 19 not given sulfonamide drugs it recurred in 42 per cent. Of 22 treated surgically, it recurred in 27 per cent. Thus radical surgical excision seems to have given the best results.

Palmer and Ricketts³⁷⁰ report 3 instances of chronic ulcerative colitis with manifestations of generalized peritonitis, with recovery. Treatment consisted in administration of sulfonamide compounds and penicillin, together with blood transfusions and other supportive measures. The possibility of a synergistic action of the two drugs is suggested.

368. Johnson, T. A.: Diagnosis and Management of Ulcerative Colitis, *M. Clin. North America* **30**:329-335, 1946.

369. Barbosa, J. de C.; Bargaen, J. A., and Dixon, C. F.: Regional Segmental Colitis, *S. Clin. North America* **25**:939-968, 1945.

370. Palmer, W. L., and Ricketts, W. E.: Chronic Ulcerative Colitis with Generalized Peritonitis and Recovery, *Arch. Surg.* **51**:102-105 (Sept.) 1945.

An 18 year old youth with a history of diarrhea since the age of $2\frac{1}{2}$, who appeared five years younger than his stated age, was admitted to the hospital with intestinal obstruction.³⁷¹ The patient did not survive the ileostomy carried out in an effort to decompress the bowel. Post-mortem examination revealed extensive chronic ulcerative colitis and a stricture of the descending colon produced by an adenocarcinoma. The testis and epididymis were infantile.

Five patients with chronic ulcerative colitis were treated by Korostoff and King³⁷² with penicillin in dosages of 30,000 units every three hours for five days up to a total of 1,200,000 units. Within one week after the completion of therapy rectal ulcerations disappeared in each case. However, in 1, residual pinpoint hemorrhages, slight edema, hyperemia, friability and granularity persisted. In another residual mild friability and hyperplastic granulations were noted. An adequate follow-up study had not been made at the time of publication. We are of the opinion that the original concept that penicillin is of no value in ulcerative colitis may require modification. Certainly, the antibiotic does not provide a specific cure for the disease. On the other hand, this preliminary report and our experience do suggest that in some cases penicillin may be of value. The psychotherapeutic effect is difficult to evaluate. Further studies are needed.

Gill³⁷³ supplements a previous communication by reporting the results of the administration of raw pig's intestinal mucosa in 17 additional cases. Of 5 patients given $\frac{1}{2}$ pound (240 Gm.) of uncooked pig's small intestine daily by mouth, 3 became well and 2 showed no improvement. There was no follow-up. Three patients failed to complete the treatment. Four patients were treated in the same manner as in the case previously reported with "preparation B" (desiccated defatted intestinal mucosa); 3 became well and 1 died in ten days with perforation of the colon. In 5 patients treated with intramuscular injections of an extract the results were not convincing to the authors and far less so to us, who conclude that no further studies are indicated.

Forty afebrile patients with chronic nonspecific ulcerative colitis were given intravenous injections of typhoid vaccine every other day for ten injections by Wilkinson and Smith.³⁷⁴ A temperature of 101

371. Ricketts, W. E.; Benditt, E. P., and Palmer, W. L.: Chronic Ulcerative Colitis with Infantilism and Carcinoma of the Colon, *Gastroenterology* 5:272-280, 1945.

372. Korostoff, B. B., and King, H. E.: Penicillin Therapy in Ulcerative Colitis: A Preliminary Report, *Am. J. M. Sc.* 211:293-298, 1946.

373. Gill, A. M.: Intestinal Mucosa in Ulcerative Colitis, *Lancet* 2:202-204, 1945.

374. Wilkinson, S. A., and Smith, F. H.: Intravenous Typhoid Vaccine Therapy in the Management of Ulcerative Colitis, *Gastroenterology* 6:171-175, 1946.

or 103 F. was considered desirable after the injection. Of the group, 27, or 68 per cent, were greatly improved; 10, or 25 per cent, were moderately improved, and 3, or 7 per cent, were not improved. During an eighteen-month follow-up 20, or 50 per cent, remained greatly improved or markedly relieved; 11, or 28 per cent, were slightly improved, and 4, or 10 per cent, showed no improvement. Three required ileostomy (7 per cent), and 2 (5 per cent) died. The average age of the group was 28.5 years. The method of treatment was applicable to 50 per cent of the patients not given surgical treatment. Follow-up fever therapy every two to four weeks was advised and used in those responding. In this study also control tests seem to us to be needed because of the recognized spontaneous tendency to remission in this disease and, furthermore, because of the difficulty in measuring the role of the coincidental psychotherapy.

A mortality rate of 8 per cent in 25 patients with nonspecific ulcerative colitis treated surgically at the University of Minnesota Hospitals is reported by Dennis,³⁷⁵ as contrasted with a mortality of 28 per cent in 57 patients treated conservatively over a ten year period ending Jan. 1, 1944. The conclusion is reached that ileostomy is indicated in all forms of chronic ulcerative colitis except the mild ones and that about one half of the patients will subsequently need a colectomy. We are unable to understand such a high mortality in the patients treated conservatively; perhaps a large number with mild forms of the disease are overlooked.

Corbett³⁷⁶ confines the number in which there are indications for surgical treatment to 15 per cent. The response to ileostomy is good; it appears more efficient in arresting the disease than appendicostomy, cecostomy or colostomy. Irrigation of the bowel is of no value.

Glenn and Read³⁷⁷ report an attack of ulcerative colitis in a 22 year old white man with ischiorectal abscess from which tubercle bacilli were isolated. There was no active pulmonary tuberculosis. The tubercle bacilli, found twice only in the course of many examinations; on the eighty-fourth and ninety-sixth days in the hospital, were demonstrated by smear and culture. Death was due to peritonitis. Several small fistulous openings in the wall of the rectum communicated with a large abscess filling the left ischiorectal fossa.

375. Dennis, C.: Ileostomy and Colectomy in Chronic Ulcerative Colitis, *Surgery* 18:435-452, 1945.

376. Corbett, R. S.: A Review of the Surgical Treatment of Chronic Ulcerative Colitis, *Proc. Roy. Soc. Med.* 38:277-290, 1945.

377. Glenn, P. M., and Read, H. S.: Tuberculous Ulcerative Colitis or Ulcerative Colitis with Superimposed Tuberculous Infection, *Gastroenterology* 6:9-20, 1946.

COLON

Physiology.—Weeks³⁷⁸ reports some interesting and significant observations made in an Arab soldier with a shrapnel wound perforating the colon and necessitating a transverse colostomy. A traumatic wound in the lower part of the abdomen, unrepaired and containing several loops of small bowel (ileum) and sigmoid, afforded an unusual opportunity to study the simultaneous effect of stimuli on the small and large bowel. Administration of neostigmine caused considerable activity in the small intestine and only slight activity in the colon. Betahypophamine caused active peristalsis of the transverse and sigmoid colon and a mild stimulation of the ileum. Morphine was a mild stimulant of the small bowel; no effect was seen on the large bowel. Ingestion of food resulted in moderate activity of the small bowel. Excitement caused notable peristalsis of the small bowel and evacuation of feces from the transverse colostomy opening. Application of hot and cold water bags to the surface of the abdomen had no effect. Spinal anesthesia greatly increased the tone of the entire bowel. Intravenous injection of hypertonic solution of dextrose had almost no effect, and intravenous injection of hypertonic solution of sodium chloride stimulated the small bowel. Calcium gluconate administered intravenously did not calm the peristalsis already present and atropine alone had no effect.

Arendt,³⁷⁹ studying the function of the colon, emphasizes the difference between the left and right colon. "Cannon's point" in the proximal third of the transverse colon, corresponding with a contraction ring seen in certain animals, is considered roentgenologically identifiable in man and important as the pivoting point in the innervation of the bowel between the vagus and the plexus nerve and, on the sympathetic side, between the superior and the inferior splanchnic nerve. Both units may be harmonious or antagonistic.

McKenney³⁸⁰ states that the addition of two or more glasses of water to meals generally obviates the necessity of remedies for constipation. We suggest that the same statement may be made of a normal diet.

Abdominal Pain as an Epileptic Equivalent.—Moore³⁸¹ describes the paroxysmal abdominal pain seen in 6 patients (2 children and

378. Weeks, D. M.: Observations of Small and Large Bowel Motility in Man, *Gastroenterology* **6**:185-190, 1946.

379. Arendt, J.: The Significance of Cannon's Point in the Normal and Abnormal Functions of the Colon, *Am. J. Roentgenol.* **54**:149-155, 1945.

380. McKenney, J. A.: The Physiologic Use of Water in Constipation, *Am. J. Digest. Dis.* **13**:78-80, 1946.

381. Moore, M. T.: Paroxysmal Abdominal Pain, *J. A. M. A.* **129**:1233-1240 (Dec. 29) 1945.

4 adults) and, on the basis of the pattern of symptomatology, the electroencephalography and the response to anticonvulsive drugs, considers it to be an epileptic equivalent. Three of the patients gave a history of antecedent injury to the head. One had cerebral angioneurotic edema following injection of antiserum prior to the onset of the abdominal seizures, 1 had paroxysmal abdominal pain, diagnosed as intestinal tetany, occurring in an unrecognized attack of tuberous sclerosis and in 1 there was no apparent etiologic background. Moore emphasizes the need for the recognition of unexplained paroxysmal pain as of possible cerebral origin and due to abnormal cerebral discharges arising in the premotor or parietal areas. The criteria of diagnosis are: (1) exclusion of intrinsic visceral disease; (2) adequate historical data; (3) pattern of attack of an epileptic order; (4) associated epileptic manifestations; (5) objective evidence of cerebral organic disease of dysfunction, and (6) effect of anticonvulsive drugs on the abdominal pain and on the electroencephalogram.

Porphyria.—Stiles, Pike and Berne³⁸² describe a 24 year old soldier who died of acute porphyria. In the early stages of the illness attention was centered on the abdominal symptoms and the leukocytosis; the importance of the neurologic picture was overlooked. There was a history of recurrent attacks of abdominal pain, nausea and vomiting and of the passage of red urine. The neurologic manifestations consisted in weakness, paresthesias, ascending paralysis, mental changes and terminal bulbar symptoms.

Megacolon.—Galambos and Mittelman-Galambos³⁸³ note that simple redundancy of the colon usually is an incidental finding only, without symptoms or complaints.

Muehsam³⁸⁴ discusses the modern concepts of congenital megacolon (Hirschsprung's disease). Bailey and Haber³⁸⁵ noted moderate improvement only in the fifteen postoperative months after ganglionectomy of the left sympathetic chain with resection of the second, third and fourth lumbar ganglions. Cattell and Colcock³⁸⁶ conclude that lumbar sympathectomy as the only operative procedure offers little chance of permanent relief and should be reserved for milder cases

382. Stiles, M. H.; Pike, G. M., and Berne, E. L.: Diagnosis of Acute Porphyria, *Northwest Med.* **45**:166-169, 1946.

383. Galambos, A., and Mittelman-Galambos, W.: Redundancy of the Colon, *Am. J. Digest. Dis.* **13**:87-101, 1946.

384. Muehsam, E.: Modern Concept of Congenital Megacolon (Hirschsprung's Disease), *Am. J. Digest. Dis.* **13**:3-9, 1946.

385. Bailey, H., and Haber, J.: Megacolon, with a Brief Review of Etiological Factors and Treatment, *Am. J. Surg.* **69**:253-257, 1945.

386. Cattell, R. B., and Colcock, B. P.: Congenital Megacolon, *S. Clin. North America* **26**:644-655, 1946.

with diffuse dilatation. It may be combined with segmental resection but should not accompany subtotal colectomy. Two patients observed for six years did not do well. The operation of choice is segmental or subtotal colectomy. The best results are obtained when the dilatation does not involve the rectosigmoid and rectum.

A volvulus of the sigmoid in a megacolon was reduced by a barium enema, according to Melamed.³⁸⁷

Volvulus.—Griffin, Bartrone and Meyer³⁸⁸ describe 7 instances of acute volvulus and 18 of subacute volvulus. The single most helpful diagnostic aid was the roentgenologic examination. Because of the tendency to recur, simple detorsion is not the treatment preferred but rather exteriorization and second stage resection.

Corff³⁸⁹ reports an unusual case of volvulus and gangrene of the sigmoid complicated by schistosomiasis. In the patients seen by Simon, Senturia and Keller³⁹⁰ the symptoms consisted in backache and an ineffectual urge to defecate, with no abdominal pain, tenderness or distention. Roentgenograms confirmed the diagnosis.

Diverticulosis and Diverticulitis.—Formation of diverticular pouch is fully discussed by Galambos and Mittelman-Galambos.³⁹¹ The problem of causation is dismissed with the conclusion that it is related to other manifestations of advancing age. The process is a slow one, developing silently and uneventfully until interrupted by some "inflammatory accident" represented by diverticulitis and its complications.

Cave and Wilson³⁹² in eleven and a half years encountered 131 patients with diverticulitis; 39 were submitted to operation and 6 died, a mortality of 15.3 per cent. The average age was 51 years. Thirteen had tenderness and spasm of the left lower abdominal quadrant and 5 in the right lower quadrant. The most frequent complication requiring surgical intervention was abscess with local peritonitis, although acute perforation with generalized peritonitis did occur. Cecostomy is considered safer than colostomy in acute obstruction.

387. Melamed, A.: Volvulus of Megacolon Reduced During Barium Enema Examination, *Radiology* **45**:392-395, 1945.

388. Griffin, W. D.; Bartrone, G. R., and Meyer, K. A.: Volvulus of the Sigmoid Colon: Report of Twenty-Five Cases, *Surg., Gynec. & Obst.* **81**:287-294, 1945.

389. Corff, M.: Volvulus and Gangrene of the Sigmoid Complicated by Manson's Schistosomiasis, *Pennsylvania M. J.* **49**:632-636, 1946.

390. Simon, H. E.; Senturia, H. R., and Keller, T. B.: Volvulus of the Sigmoid Colon, *Am. J. Surg.* **71**:550-552, 1946.

391. Galambos, A., and Mittelman-Galambos, W.: Diverticulosis and Diverticulitis of the Colon, *Rev. Gastroenterol.* **13**:171-194, 1946.

392. Cave, H., and Wilson, E. A.: Diverticulitis of the Colon, *S. Clin. North America* **26**:390-396, 1946.

Two cases of solitary diverticulitis of the cecum diagnosed preoperatively as acute appendicitis are reported by Gatewood.³⁹³

Peritonitis.—Siegal³⁹⁴ describes 5 cases of benign paroxysmal peritonitis and tabulates 5 more from the literature. The picture is that of recurrent paroxysms of severe abdominal pain, with a temperature as high as 105 F., severe prostration and evidence of peritoneal irritation. Diarrhea is conspicuously absent, and leukocytosis is frequent. Siegal suggests that the condition is a manifestation of the "erythema group" of Osler and perhaps an allergic phenomenon due to sensitization to foods, but there is no definite evidence for this concept.

Analysis at autopsy by Weinberger³⁹⁵ in 19 deaths from perforation of the colon disclosed that in 10 the primary lesion was diverticulitis, in 7 a malignant process and in 2 perforation from mechanical agents, one an enema.

Black and Evert³⁹⁶ find that in malignant processes in the colon free perforation is most commonly associated with complete obstruction. Obstructing carcinoma is commoner in the left side of the colon, particularly in the sigmoid and rectosigmoid. The perforation in 3 cases was situated at or near the obstructing lesion. The prognosis is poor. Hendelberg,³⁹⁷ in reviewing the cancers of the colon in patients under 35 years of age treated at the University of Uppsala, found 6 patients admitted with distinct signs of perforation, yet with no basis for the diagnosis of cancer preoperatively.

One fatal peritonitis from a fistula complicating lymphopathia venereum is reported.³⁹⁸

Anthony³⁹⁹ describes tuberculous peritonitis seen in 4 prisoners of war. The patients were all young adults; 2 gave a history of the prolonged consumption of raw milk.

Injury of the Rectum.—Pratt and Jackman⁴⁰⁰ review twenty perforations of the rectum by enema tips as reported in the literature

393. Gatewood, J. W.: Solitary Diverticulitis of the Cecum, *Ann. Surg.* **122**:52-58, 1945.

394. Siegal, S.: Benign Paroxysmal Peritonitis, *Ann. Int. Med.* **23**:1-21, 1945.

395. Weinberger, H. A.: Observations on Large Bowel Perforations, *Surgery* **18**:547-555, 1945.

396. Black, B. M., and Evert, J. A.: Peritonitis Following Malignant Obstruction of the Sigmoid and Free Perforation: Report of Three Cases, *Proc. Staff Meet., Mayo Clin.* **21**:137-142, 1946.

397. Hendelberg, T.: Perforation as the First Sign of Cancer in the Large Intestine in Young Patients, *Acta chir. Scandinav.* **92**:339-348, 1945.

398. Pearce, A. E.; Bowen, J. O., and Burns, J. C.: Fatal Peritonitis from Procto-Salpingostomic Fistula Complicating Lymphopathia Venereum, *Am. J. Surg.* **69**:406-408, 1945.

399. Anthony, P. K.: Tuberculous Peritonitis: Case Reports with Pathological Findings, *Illinois M. J.* **89**:82-85, 1946.

400. Pratt, J. H., and Jackman, R. J.: Perforation of the Rectal Wall by Enema Tips, *Proc. Staff Meet., Mayo Clin.* **20**:277-283, 1945.

and add two. There were 8 deaths and 12 survivals, a mortality rate of 40 per cent. Proctoscopy is a valuable diagnostic aid, because the perforation is usually located on the anterior rectal or rectosigmoidal wall.

Colcock⁴⁰¹ reports that in 120 patients with perforating wounds of the colon or rectum admitted to a general hospital in the Mediterranean Theater there were 4 deaths, which were due to pulmonary embolus, multiple abdominal abscesses following retraction of a cecostomy, exsanguinating hemorrhage from a divided gastroduodenal artery and persistent suppuration in the retroperitoneal tissues without response to surgical drainage or chemotherapy. Adequate transfusions of blood, antibiotics and increased surgical skill account for the decreased morbidity and mortality. Shidler⁴⁰² lists 10 cases in which there was no mortality and stresses the importance of considering abdominal perforation in the presence of gluteal wounds. Death usually ensues if the interval of time between intestinal injury and operation is more than eighteen hours. Croce⁴⁰³ describes 2 additional cases. Blaisdell⁴⁰⁴ discusses traumatic injuries and their treatment.

In Walker's⁴⁰⁵ 28 year old soldier with amebiasis signs of perforation of the rectum developed after sigmoidoscopy. At operation the tear was closed; the postoperative course was stormy. Cysts of *Entamoeba histolytica* were found in the peritoneal drainage.

Spontaneous rupture of the sigmoid with evisceration of the small intestine through the anal orifice, the seventh such case to be reported in the literature, is described by McLanahan and Johnson.⁴⁰⁶ In 6 cases there was a preexisting rectal prolapse; in the seventh the condition followed trauma.

Vaughn and Martin⁴⁰⁷ found a knife 9.5 inches (about 24 cm.) long in the sigmoid.

After a therapeutic abortion during the fourth month of pregnancy, sepsis, pelvic inflammation and diarrhea developed; fetal bones were

401. Colcock, B. P.: Injuries of the Colon and Rectum, *S. Clin. North America* **26**:665-668, 1946.

402. Shidler, F. P.: Abdominal War Wounds, *U. S. Nav. M. Bull.* **46**:558-565, 1946.

403. Croce, E. J.: Perforating Wounds of the Rectum, *S. Clin. North America* **26**:397-401, 1946.

404. Blaisdell, P. C.: Traumatic Injuries of the Rectum, *J. A. M. A.* **128**: 559-563 (June 23) 1945.

405. Walker, H. B.: Sigmoidoscopy: Perforation of the Rectum, *Brit. M. J.* **1**:434, 1946.

406. McLanahan, S., and Johnson, M. L.: Spontaneous Rupture of Lower Colon with Evisceration of Small Intestine Through the Anal Orifice, *Surgery* **18**:478-482, 1945.

407. Vaughn, A. M., and Martin, J. A.: Foreign Body (Case Knife) in the Sigmoid, *J. A. M. A.* **130**:29-30 (Jan. 5) 1946.

passed rectally. Operation later by Fruhlinger⁴⁰⁸ disclosed an abscess between the rectum and the uterus; a fecal fistula of the abdominal wall was still present fourteen months postoperatively.

Lymphopathia Venereum.—Savignac⁴⁰⁹ reports complete inflammatory obliteration of the rectum from lymphopathia venereum.

External Fistula.—Dixon and Benson⁴¹⁰ discuss the principles in the management of external fecal fistulas; 65 patients were submitted to operation, with a mortality of 3 per cent. In the great majority the fistulas had as their point of origin the ileum, cecum or sigmoid. In 97 per cent the fistula followed some type of operative procedure.

Jackman and Buie⁴¹¹ report a series of 600 cases of anal fistulas. In 88.5 per cent no tuberculosis was demonstrable either in the fistulas or elsewhere in the body; in 11.5 per cent evidence of tuberculosis was found somewhere in the body. In 3 cases (0.5 per cent) inoculation of a guinea pig with material from a fistula gave a positive result, in 2 cases (0.3 per cent) histologic examination only revealed the disease and in 6 cases (1 per cent) both procedures revealed the disease. It is apparent, therefore, that a relatively small number (7 to 8 per cent) of anal fistulas are tuberculous; in nearly all these (thirty-three out of thirty-nine) there is an unmistakable tuberculous focus elsewhere in the body.

Pruritus Ani.—A study by Shapiro and Rothman⁴¹² of 70 patients with pruritus ani revealed none of the commonly listed etiologic factors. Neurodermatitis was present in 55.7 per cent. Rubbing with paper is considered to be the factor initiating or perpetuating the itching-scratching cycle. Treatment is based on the elimination of the use of toilet paper, the substitution of a superfatted soap sitz bath, the auxiliary use of phenobarbital, local application of ointments or lotion and minimal doses of roentgen rays. It was successful in 93.1 per cent of the 58 patients on whom a follow-up could be made. Bodkin⁴¹³ reports good results with a formula containing "taka diastase" and diphenylhydantoin sodium given by mouth in a series of 42 cases.

408. Fruhlinger, B.: Fetal Bones Passed in the Feces, *Am. J. Surg.* **70**:126-127, 1945.

409. Savignac, R.: Un nouveau cas d'obliteration complete d'une stenose inflammatoire du rectum, *Arch. d. mal. de l'app. digestif* **35**:77-80, 1945.

410. Dixon, C. F., and Benson, R. E.: Principles in the Management of External Fecal Fistulas, *J. A. M. A.* **130**:755-761 (March 23) 1946.

411. Jackman, R. J., and Buie, L. A.: Tuberculosis and Anal Fistula, *J. A. M. A.* **130**:630-632 (March 9) 1946.

412. Shapiro, A. L., and Rothman, S.: Pruritus Ani: A Clinical Study, *Gastroenterology* **5**:155-168, 1945.

413. Bodkin, L. G.: Oral Therapy for Pruritus Ani, *Am. J. Digest. Dis.* **12**:255-257, 1945.

Benign Tumors.—Lust ⁴¹⁴ reports a benign single polyp. Pfeiffer and Patterson ⁴¹⁵ describe 5 instances of congenital polyposis of the colon and emphasize the tendency of these lesions to undergo malignant changes. The condition is predominantly hereditary.

Delannoy ⁴¹⁶ depicts a submucous lipoma of the ascending colon producing a latent ileoceccocolic invagination.

Endometriosis.—Klossner ⁴¹⁷ describes heterotopia endometriosis in the sigmoid flexure, diagnosed on gross inspection by the gynecologist at the first operation for a pelvic tumor as a carcinoma of the sigmoid. At the second operation microscopic examination disclosed the true diagnosis.

Sarcoma.—Herly ⁴¹⁸ reports that paraffin pellets containing 1 mg. of methyl-cholanthrene introduced into the abdominal cavity of young adult male C57 mice produced ascites in fifty days and sarcomas in all mice surviving for ninety days. The ascitic fluid, even when obtained before the development of sarcomas, produced ascites and malignant tumors when injected intra-abdominally into another series of the same strain. The ascitic fluid obtained from this second series when injected intra-abdominally into a third series of mice again resulted in ascites and sarcomas. These tumors were transplantable by subcutaneous inoculation. Whatever the active agent may have been, it was destroyed by ether and by exposure to a temperature of 90 C.

Seven new lymphosarcomas of the digestive tract are presented by Moreton.⁴¹⁹ The roentgenologic findings resembled carcinoma in all instances; the diagnosis was made by exploratory operation and biopsy. Three tumors occurred in the stomach and three in the ileum, and one involved both the stomach and the rectum.

Resection of a spindle cell sarcoma of the rectal wall is described by Goldman and Marbury.⁴²⁰ The patient was alive seven months later.

414. Lust, F. J.: Roentgenological Diagnosis of Benign Tumors (Single Polyps) of the Colon, *Am. J. Roentgenol.* **54**:276-281, 1945.

415. Pfeiffer, D. B., and Patterson, F. M.: Congenital or Hereditary Polyposis of the Colon, *Ann. Surg.* **122**:606-624, 1945.

416. Delannoy, E.: Invagination ileo-caeco-colique latente par lipome sous-muqueux du colon ascendant, *Arch. d. mal. de l'app. digestif* **34**:329-333, 1945.

417. Klossner, A. R.: Sur l'endométriose se présentant dans l'anse sigmoïde, *Acta chir. Scandinav.* **93**:254-269, 1946.

418. Herly, L.: Intraperitoneal Sarcomas Produced in Mice with Mouse Ascitic Fluid, *Cancer Research* **6**:131-133, 1946.

419. Moreton, R. D.: Lymphosarcoma with Primary Manifestations in the Gastro-Intestinal Tract, *Texas State J. Med.* **41**:458-464, 1946.

420. Goldman, M. L., and Marbury, W. B.: Sarcoma of the Rectum. *Am. J. Surg.* **71**:387-391, 1946.

Carcinoma.—Dunham, Nichols and Brunschwig⁴²¹ have shown that cancerous mucosa contains less calcium and more potassium than adjacent normal mucosa. In papillomas of the colon an increase in potassium of the same order as that found in carcinoma was observed, but the degree of reduction in calcium was not so pronounced as in the latter.

In a study of the location of colonic cancer in 1,457 patients from 1936 through 1944 Boehme and Hanson⁴²² found that 6.52 per cent (95) were cecal and that 3.30 per cent (48) were in the ascending colon, 2.94 per cent (43) in the hepatic flexure, 4.51 per cent (66) in the transverse colon, 2.4 per cent (34) in the splenic flexure, 3.97 per cent (58) in the descending colon, 12.42 per cent (181) in the sigmoid, 53.32 per cent (777) in the rectum and 0.06 per cent (9) in the anus. Thus 75 per cent of all colonic carcinomas were located in the sigmoid, rectosigmoid or rectum.

Rewell⁴²³ reports two carcinomas of the rectum in sisters aged 29 and 32. One had multiple polyposis of the colon and the other multiple telangiectasis. Casco Muñoz⁴²⁴ describes 2 patients with multiple simultaneous tumors of the large bowel.

Swinton and Gillespie,⁴²⁵ in an analysis of symptoms and diagnosis, found that the average time from the onset of symptoms to operation was nine months. In 100 patients with carcinoma of the right colon 87 per cent complained of abdominal cramps, indigestion or pain; only 9 had gross blood in the stools. Eighty per cent of patients with neoplasm of the left colon complained of change in the normal bowel habit; 30 per cent had frequent loose stools or diarrhea. In respect to patients with rectal neoplasms 86 per cent complained of abnormality of the stools in the form of pus, blood, mucus and sometimes a change in the caliber. Fifty per cent of the patients with benign mucosal tumors noted bleeding. Seventy per cent of the polyps can be visualized with a 10 inch (25.4 cm.) sigmoidoscope. Berk⁴²⁶ discusses the findings in 21 patients with proved cancer of the colon and rectum in army general hospitals.

421. Dunham, L.; Nichols, S., and Brunschwig, A.: Potassium and Calcium Content of Carcinoma and Papillomas of the Colon, *Cancer Research* 6:233-234, 1946.

422. Boehme, E. J., and Hanson, P. J.: Carcinoma of the Colon and Rectum: Site of Growth of 1,457 Lesions, *S. Clin. North America* 26:551-552, 1946.

423. Rewell, R. E.: Carcinoma of the Rectum in Sisters, *Brit. M. J.* 1: 683, 1946.

424. Casco Muñoz, E. D.: Carcinomas múltiples y simultáneos del intestino grueso, *Rev. Asoc. méd. argent.* 59:1031-1033, 1945.

425. Swinton, N. W., and Gillespie, J. L.: The Diagnosis of Carcinoma of the Colon and Rectum, *S. Clin. North America* 26:553-563, 1946.

426. Berk, J. E.: Carcinoma of the Colon and Rectum, *M. Clin. North America* 30:307-328, 1946.

Dixon and Benson⁴²⁷ review the records of 64 patients with carcinoma of the sigmoid or rectosigmoid involving the urinary bladder. Extensive resections were performed in 40, with 7 operative deaths. Twenty of the 40 were still living; survivals ranged from less than one to more than five years, and 7 had lived for five or more years.

Surgical mortality rates and the merits of various operations are reviewed by numerous authors. Many helpful suggestions are given. Thus Bohme and Cattell⁴²⁸ believe that in most cases it is wise to avoid preoperative discussion of colostomy. They consider that in the management of a colostomy gauze bandages with a 6 inch wide (15 cm.) elastic belt are preferable to a colostomy bag. Pfeiffer and Levering,⁴²⁹ in 179 cases, note a gross over-all mortality of 20.1 per cent; in favorable cases with operation of considerable magnitude the mortality was 5.5 per cent. Meyer and his associates⁴³⁰ report twenty one stage resections of the left half of the colon by an "open" technic, with a mortality of 5 per cent. In 25 private patients primary resection and anastomosis were performed, with a 4 per cent mortality.⁴³¹ In McMillan's⁴³² 27 cases in which he used a one stage procedure with end to end anastomosis and without preliminary cecostomy the single death was due to a pulmonary complication. Cattell and Colcock⁴³³ report that a modified Mikulicz resection employed in 450 patients gave a mortality of 11 per cent. In 1945, 84 patients with carcinoma of the colon were explored; resections were performed in 77, in 62 by a two stage modified Mikulicz procedure. Of the 77, 39 per cent had lesions of the right colon, with primary resection in 13. There was no operative mortality in the 13. Shier⁴³⁴ discusses the technic of resection of the right colon.

427. Dixon, C. F., and Benson, R. E.: Carcinoma of Sigmoid and Rectosigmoid Involving Urinary Bladder, *Surgery* 18:191-199, 1945.

428. Bohme, E. J., and Cattell, R. B.: Cancer of the Rectum: A Discussion of Preoperative Preparation, Postoperative Complications and Colostomy Management, *S. Clin. North America* 26:564-573, 1946.

429. Pfeiffer, D. B., and Levering, J. W.: Carcinoma of the Large Bowel: A Review of Cases Treated by the Pfeiffer Surgical Clinic over a Five-Year Period, 1939 to 1943 Inclusive, *Clinics* 4:27-35, 1945.

430. Meyer, K. A.; Sheridan, A., and Kozoll, D. D.: One Stage "Open" Resection of Lesions of the Left Colon Without Complementary Colostomy, *Surg., Gynec. & Obst.* 81:507-514, 1945.

431. Meyer, K. A., and Kozoll, D. D.: Primary Resection of the Colon with Special Reference to Diagnosis and Management, *S. Clin. North America* 26:176-199, 1946.

432. McMillan, W. M.: Primary Resection of Malignant Lesions of the Large Bowel, *Am. J. Surg.* 71:502-504, 1946.

433. Cattell, R., and Colcock, B. P.: Primary Resection of the Right Colon, *S. Clin. North America* 26:606-609, 1946.

434. Shier, R. V. B.: Right Colon Resection, *Canad. M. A. J.* 53:18-20, 1945.

Of 461 patients with carcinomas of the anus, rectum and sigmoid, 424 were submitted to operation by Bacon.⁴³⁵ In 371, 80 per cent of the original group, resection was accomplished without loss of the anal sphincter. In 262 (70 per cent of those resected) abdominal colostomy was not performed. In the 236 cases in which the proctosigmoidectomy of Babcock was employed the mortality was 6.3 per cent. Peritonitis was the chief cause of death. Jenkins⁴³⁶ discusses the preservation of sphincter control.

Lahey⁴³⁷ regards complete removal of the tumors as more important than maintenance of an intact rectal sphincter. In his experience, 83.5 per cent of the rectosigmoidal tumors were resectable, with a 3.8 per cent mortality. There was no recurrence in five years in 50 per cent. Hayden⁴³⁸ reports that in 198 patients with carcinomas of the rectum treated with radical resection the total mortality rate was 13 per cent; in those treated with the single stage abdominoperineal resection it was 10 per cent. Of the 98 patients subjected to operation five or more years prior to the study, 32 (33 per cent) were still alive.

Succinylsulfathiazole was found by Behrend⁴³⁹ to be nontoxic when given in large doses and effective in reducing the incidence of peritonitis and infection. Newton and Blodgett⁴⁴⁰ report a comparison of seventy-eight resections without preoperative administration of succinylsulfathiazole and postoperative intestinal suction and thirty-six similar resections in patients receiving such treatment. The incidence of postoperative infection was reduced from 43 to 6 per cent and the mortality from 22 to 3 per cent.

Postoperative anemia and circulatory collapse reported by Bartels⁴⁴¹ were corrected by restoration of the fluid and salt balance. Approximately 7 Gm. of salt is lost with each 1,000 cc. of ileostomy fluid.

435. Bacon, H. E.: Abdominoperineal Proctosigmoidectomy for Cancer of the Rectum: Conclusions Based on Five-Year Experience, *Am. J. Surg.* **71**:728-742, 1946.

436. Jenkins, J. A.: Carcinoma of the Rectum, with Special Reference to Sphincteric Control, *Australian & New Zealand J. Surg.* **15**:15-24, 1945.

437. Lahey, F.: Selection of Operation and Technic of Abdominal Perineal Resection for Carcinoma of the Rectum, *S. Clin. North America* **26**:528-552, 1946.

438. Hayden, E. P.: The Surgical Treatment of Carcinoma of the Rectum; Statistics on One Hundred and Ninety-Eight Cases of Carcinoma, *New England J. Med.* **233**:81-84, 1945.

439. Behrend, M.: Colon Surgery and the Sulfonamide Drugs with Especial Reference to Elimination of Mikulicz Operation, *J. A. M. A.* **128**:9-12 (May 5) 1945.

440. Newton, F. C., and Blodgett, J. B.: Succinylsulfathiazole and Intestinal Suction in Surgery of the Large Bowel, *Surgery* **18**:200-206, 1945.

441. Bartels, E. C.: Anuria and Uremia Following Surgery of the Right Colon, *S. Clin. North America* **26**:628-630, 1946.

As one looks back over the history of cancer of the colon in the past two or three decades, several points seem clear. In the first place, there has been relatively little advance in our knowledge of the cause of cancer, in the mechanism of its spread or in other pathologic features. The development and general use of the roentgenologic method and proctosigmoidoscopy have greatly increased the ease of diagnosis and, while reliable data are not available, seem surely to have brought about earlier diagnosis. Surgical technics have improved enormously; however, the failure of the surgeons to agree on the best methods for dealing with lesions in various locations is clear evidence that the end of this developmental era has not yet been reached. Mortality rates have dropped steadily because of a combination of factors: improved surgical technics; better methods of anesthesia; more careful preoperative preparation, including attention to the plasma protein content and to the fluid and electrolyte balance; the prompt and effective use of blood and plasma to prevent and counteract shock; the prevention of gastric and intestinal distention by routine use of Wangensteen gastric drainage, and, last but not least, the introduction of the antibiotics, the sulfonamide drugs and penicillin. And so, while the search for the cause of cancer is being continued, it is a mistake to overlook or minimize the tremendous therapeutic advances already made or to think that the end of the road has been reached; the maximum that can be accomplished with present available resources is not yet known.

Book Reviews

Carbohydrate Metabolism: Correlation of Physiological, Biochemical and Clinical Aspects. By Samuel Soskin, M.D., and Rachmiel Levine, M.D. Price, \$6. Pp. 315. Chicago: University of Chicago Press, 1946.

This is an important book. It is divided into five parts, and each part is divided into several chapters. Thus, carbohydrate metabolism is discussed from many viewpoints: its biochemistry, its physiology, its abnormal physiology in diabetes and other endocrine disorders and the manner in which its clinical and physiologic aspects can be integrated. At the end of each chapter is an active bibliography; in all, more than twelve hundred references are cited, so that a reader can easily follow, in greater detail than have the authors, any trail in carbohydrate metabolism which happens to interest him.

The various tables and illustrations are easily understood, and the printing is good. Best of all, the language is simple and direct, so that even the complicated intricacies of enzyme chemistry are made understandable.

The authors state that their work is intended to serve as a correlative text for the teaching of the subject to students of physiology, biochemistry and medicine. They seem to have filled this large order adequately; their publication promises to be a standard source of reference.

Cardiovascular Disease in General Practice. (General Practice Series). By Terence East, D.M. (Oxon.), F.R.C.P. (Lond.). Second edition. Price, 12s. 6d. Pp. 198, with 40 illustrations. London: H. K. Lewis & Co., Ltd., 1946

The ARCHIVES reviewed the first edition of this book (63:1235 [June] 1939), characterizing it as readable and worth meeting. The second edition is as good as the first, a little more up-to-date and continuing to give an admirable clinical discussion of various phases of cardiac disease and its management. New procedures are described, such as the surgical attack on certain cardiac diseases and the treatment of subacute bacterial endocarditis with sulfonamide drugs or penicillin. The electrocardiogram is mentioned more frequently. The volume as a whole hews to the old line, attempting to evaluate the difficulties oftenest met in general practice and to show how they often may be overcome by relatively simple means. It is interesting to have the British viewpoint on such matters.

Glomérulo-nefrite aguda difusa no Distrito Federal (Estudos de 116 Casos). (Acute Diffuse Glomerular Nephritis in the Federal District). By Francisco Arduino and Romeu H. Loures. Volume 1, No. 2. Rio de Janeiro: Arquivos de Clínica, 1945.

In the present work 116 cases of acute diffuse glomerular nephritis are studied, taken from seven hospitals in the Federal District (Brazil). These cases are analyzed with reference to occurrence, etiology, clinical picture, renal function, blood chemistry, evolution and treatment.

The disease was about the same in both sexes, and the frequency was greatest between the ages of 11 and 35. The incidence was highest during the cold months of the year. The main causes of acute diffuse glomerular nephritis in hospitalized patients were observed to be infections of the skin (impetigo) and infections of the lymphoid tissue of the throat.

The mode of onset in order of frequency was as follows: edema, headache, dyspnea, pain in the lumbar region, oliguria, anuria and purpura. Subcutaneous edema was present in practically all cases. The average blood pressure was observed in 70 per cent of the cases. Autopsies were performed in 4 cases.

This study shows that the incidence, the course and the prognosis of acute diffuse glomerular nephritis in Brazil are similar to those in studies made in the United States. This is an interesting monograph and well worth reading.

Exercises in Human Physiology (Preparatory to Clinical Work). By Sir Thomas Lewis. Price, \$1.25. Pp. 103, with 8 illustrations. London: The Macmillan Company, 1945.

Sir Thomas Lewis has long advocated that in addition to the usual studies in physiology the student should also be trained in human physiology as seen in the normal human subject, and that he should learn what is the normal base line from which derivation might be judged. He has stated elsewhere that all the problems of clinical practice are amenable to solution by the same physiologic line of approach that one learns in the physiology laboratory.

This little volume is a series of exercises in physiology of the normal human being. It can be recommended to the student and to his teacher, and to those in clinical practice as well.

Experimental Studies on the Effect of Sulfapyridine on Pneumococci and Gonococci. By Kai Schmith. Translated from Danish by Hans Andersen, M.D. Pp. 216. Copenhagen, Denmark: NYT Nordisk Forlag, Arnold Busck, 1941.

This is a booklet covering the author's experimental work on pneumococci and gonococci performed at the State Serum Institute, Copenhagen, Denmark, from 1938 to 1940. It includes (1) an introduction, which reviews the results in Denmark of the treatment of pneumococcic infections with type-specific serum and sulfapyridine; (2) a historical review of the experimental research on the antibacterial effect of sulfanilamide and its derivatives; (3) five chapters that summarize the author's experiments on the (a) effect of sulfapyridine on pneumococci in vitro, showing that it does exert a bacteriostatic effect that is dependent on the medium, the inoculum and the experimental conditions; (b) effect of sulfapyridine on experimental pneumococcic infections, showing that it exerts the same bacteriostatic effect in vivo that is dependent on the dose, the duration of treatment and the type and number of organisms present and that it does not interfere with specific immunity; (c) the resistance of pneumococci to sulfapyridine, in which it is shown that organisms do develop resistance both in vitro and in vivo, that there is a pronounced variation in resistance in different strains and types and that resistance is not dependent on the antigenic structure; (d) combined sulfapyridine treatment and active or passive immunization, in which it is shown that synergism is apparent, and (e) effect of sulfapyridine on gonococci, in which it is shown that there is a decided variation in sensitivity in vitro in different strains of organisms and that this is perpetuated in clinical transfer (each chapter contains a review of previous investigative work), and (4) a summary of all investigative work by the author.

The booklet reveals careful, thorough and extensive experimental work on the effect of sulfapyridine in vitro and in vivo on the pneumococcus and its relation to serum therapy. The effect on gonococci is handled in much less detail. All experiments are well controlled, and the conclusions are compatible with experimental findings. However, the majority of the experiments merely confirm or elaborate on the results of previous investigation. Some original observations are made, such as the tendency in mice for combined therapy (serum and sulfapyridine) to produce hematuria.

The author duplicates the errors of all early investigators in this field, mainly in the use of serum and proteins in the mediums for in vitro experiments, which are now known to inhibit the action of sulfonamide drugs. Theories as to the mode of action of the sulfonamide drugs are reviewed, but no definite conclusions are drawn. All observations and conclusions add mainly to the completion of

the early data on the mode of action and effectiveness of sulfonamide therapy. They have lost present appeal, owing to the introduction of other sulfonamide derivatives and the newer antibiotics.

Catgut Sterilization: The Basic Principles of the Spore-Germinating Method. By Henry M. Christensen. Pp. 174. Copenhagen, Denmark: NYT Nordisk Forlag, Arnold Busck, 1944.

This monograph comprises original investigative work on a new method of sterilization of surgical gut and a historical review of methods of sterilization of surgical gut.

The author describes a new method, known as the spore germination method. The first step is to sterilize freshly softened split and looped ribbons prior to twisting, according to the method of Kuhn. The next phase of the process concerns itself with the incubation of both anaerobes and aerobes to allow germination of all spores without the appearance of new resistant elements. After the period of cultivation, complete sterilization is then effected while the maximum number of spores are present and before new resistant spores have time to be formed. The subsequent handling of the ribbons after sterilization proceeds under simple aseptic precautions in properly equipped premises, followed by a mild after-sterilization.

The author claims that by means of this method it is possible to produce a surgical gut that is both sterile and strong, but the entire process must be carefully controlled bacteriologically, both for the incubation and the after-treatment. The author's method of incubating first anaerobically and then aerobically results in an increase in the quantity of microbes to some extent over a short time; but with the short method of incubation the quantity of microbes does not play as important a part as the fact that the bacteria and spores can be killed before they affect the quality of the material. When the spore-germinating principle is properly applied, the number of spores within reasonable limits is quite unimportant as long as they can all be killed by the subsequent process of sterilizing. It was found that 1 per cent solution of iodine at 40 C. (104 F.) will kill bacteria extremely rapidly. In the author's experiments he was able to show that during the brief period of incubation there is a reduction in the resistance to iodine of microbes in the material, whereas if the incubation is prolonged resistance to iodine increases slowly. It was shown experimentally that treatment of the ribbons with 1 per cent solution of iodine results in no appreciable loss in tensile strength. Tests of absorption in white rats showed that surgical gut made according to the spore germination principle is absorbed no more slowly than surgical gut manufactured in other ways.

This monograph should be of interest to all those concerned with the preparation and manufacture of surgical gut.

The Clinical and Prognostic Aspects of Acute Glomerular Nephritis. By Johan Rudebeck. Lund, Sweden: The Medical Clinic.

It is stated in the introduction that, notwithstanding recent advances, knowledge of the clinical aspects of acute glomerular nephritis is still incomplete. In some respects the opposite views are asserted. The author's material for this book is selected from records of cases of patients treated for glomerular nephritis in the Medical Clinic at Lund, Sweden, within a period of years from 1910 to 1939. This material comprises 356 patients over 10 years of age with no previous history of renal disease in whom an acute infection was followed by acute glomerular nephritis. One of the essential purposes of this book has been to try to settle which factors influence the prognosis of acute nephritis. Naturally, the reliability of the results obtained in this sort of an analysis is encumbered because of the impossibility of an exact estimation of the outcome in each individual case. This shortcoming, however, is admitted by the author, but this is a failing inherent in all such reports.

The cases are analyzed, and the clinical data are tabulated and discussed in a manner which gives the reader the results of the author's investigation in a

concise and satisfactory form. Many of the points taken up for study are problems which are stumbling blocks for all investigators of the diseases of the kidney. For example, the question arises as to whether all cases of chronic nephritis originate from neglected cases of acute nephritis. Then comes the discussion of the value of rest in bed and its effect on the ultimate consequence of acute nephritis. The influence of various other factors, such as tonsillectomy, diet and medication, on the prognosis is discussed. In the author's opinion none of these factors has a favorable effect, that is, statistically, on the outcome. Undoubtedly, the author says, protracted confinement to bed is of no decisive significance in the prevention of the development of chronic nephritis. Likely the physician stands but a slight chance of influencing therapeutically the late result of acute glomerular nephritis.

The material in this book is excellently analyzed, tabulated and discussed. The author modestly makes no pretense of settling the difficult problems brought up for investigation. There is a rich bibliography which comprises the important work of many authors. This book is an extremely fine addition to the world's literature on nephritis, and all physicians interested in this subject are indebted to Dr. Rudebeck for his analysis and summary of his cases on the clinical and prognostic aspects of acute glomerular nephritis.

Anais da Faculdade de Medicina da Bahia: 1944-1945. Volume IV. Pp. 398.
Salvador, Bahia, Brazil: Faculdade de Medicina da Universidade da Bahia, 1946.

This book is a volume of ten articles by the professors of the Faculty of Medicine of Bahia (Brazil). One of the most interesting is the "Clinical Study of Myocardial Infarction," with the presentation of numerous electrocardiograms and a study of electrocardiographic and clinical symptoms. The article "Rural Endemias" is a statistical study concerning the tropical diseases commoner in Bahia and their prophylaxis, such as malaria, intestinal parasites, schistosomiasis, and leishmaniasis, which are difficult medical problems in the rural zones of Brazil. The illustrations in the article on "Elephantiasis" concerning clinical cases in the state of Bahia are most interesting. In the article on "Allergy of the Newborn" the theories explaining the production of allergy in newborn infants are adequately discussed. Presentation of an interesting case of medullar schistosomiasis mansonii is surgically and pathologically confirmed in a patient who had flaccid paraplegia. This study gives numerous references to Brazilian and foreign authors. An analysis of a case of mechanical jaundice by biliary stenosis has many fine illustrations of the enlargement of the liver. The abstract on treatment of noninflammatory chronic glaucoma and another on hemorrhages of the tonsils deal with both medical and surgical phases. The last article is an analysis of the different treatments for typhoid and includes a special chapter concerning the antipyretic properties of azedinha (*Begonia bahiensis*), which is a plant that grows in Bahia.

As may be gathered from the foregoing statements, this book is well written and extensively illustrated. For persons interested in medical disorders in and about Central and South America this volume would make an excellent reference.

Undersogelser over Virkningen af thyreotrope hypofyseforlappraeparater: Med saerligt Henblik paa Strykebestemmelse og standardisering. By I. B. Andersen. Pp. 172. Copenhagen, Denmark: G. E. C. Gads Forlag, 1943.

This paper is an extension of investigations started by the League of Nations regarding the standardization and assay of the potency of thyrotropic hormone. Most of the methods which have been published were subjected to statistical analysis, but, unfortunately, histometric technics were not included. The author concludes that assay by means of the weight of the thyroid is the most suitable of those compared. The paper is written in Danish but includes an adequate English summary.

OSTEOPOROSIS ASSOCIATED WITH LOW SERUM PHOSPHORUS AND RENAL GLYCOSURIA

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WE ARE presenting the history and investigations concerning a patient with progressive decalcification, a low serum phosphorus content and renal glycosuria. The findings suggest that a physiologic defect of the renal tubules is the primary cause for certain osteoporotic conditions of obscure origin.

REPORT OF A CASE

D. L., a man aged 39 years at death, was born at St. Davids, Pembrokeshire, in 1906, the seventh child of a family of nine, the other members being four brothers and four sisters.

As a child he was considered to be healthy and strong. His father died in 1914 of a gastric ulcer, and his mother died (after World War I) of meningitis. Seven of the family are dead, six of tuberculosis and the seventh from an accident. The youngest brother is well.

When aged 22, after a severe infection of the throat stiffness developed in his back and muscles, which passed off in one month. From that time on he was in and out of employment, living on an inadequate diet and going without food on many days. In 1932 he noticed that he had difficulty in straightening himself and was having much generalized pain. He also complained of weakness of his legs, so that he occasionally stumbled and fell if he caught his foot on the ground. About this time he moved to Birmingham, and since his health had not improved he was admitted to a hospital and treated for rheumatism. Following his discharge from the hospital, he found himself no better, and after further falls he was admitted to the Birmingham Infirmary, where he was treated with sodium gold thiomalate ("myocrysin") but was unable to finish the course because of a severe cutaneous reaction. At this period (1933) he was only able to walk with the aid of two sticks. His back was painful, and during the next few years his condition gradually got worse. However, roentgenograms of the skeleton taken in 1934 revealed no abnormality of the bones, and a note in 1936 stated that no deformity of the bones was seen. In 1938, during a mild infection of the upper

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respiratory tract, with pyrexia and cough, a deformity of the sternum developed overnight. His legs became weaker, so that he was semibedridden. He was unable to raise his arms above his shoulder, and in 1939 tremor of the legs appeared. He had numerous postural aches and pains, was tender to touch and had much discomfort following muscular contractions. He had always drunk much tea, and this habit was more marked in recent years, but he did not often need a drink during the night. He micturated at 8 p. m. on retiring, again before midnight, but not again until morning. He had occasional mild cramps, with some numbness and tingling of his hands, and also periods of mental depression. He had no soreness of the tongue or mouth. His bowel habits were regular, and the stools were well formed and colored.

He had never had a large appetite and usually neglected breakfast. While out of work, though food was scarce, he had always tried to get one meal during the day; nevertheless, even when in work, he frequently missed his meals. He had never liked milk. Since the beginning of the war he had had no extra milk, and although the diet in the infirmary provided 27 ounces (755 cc.) per day, he

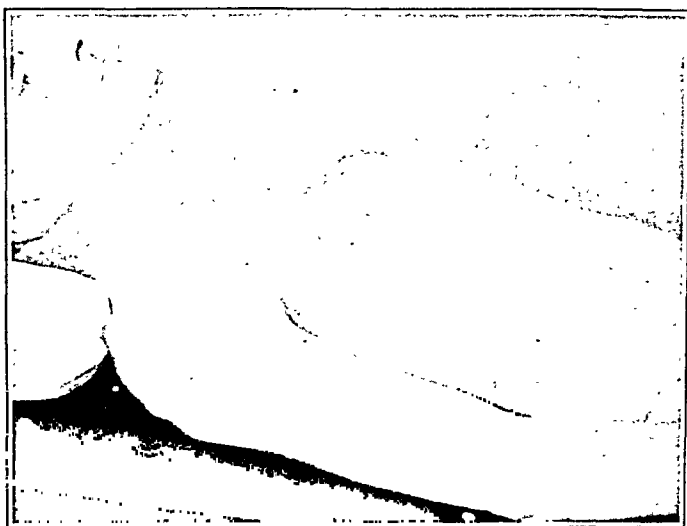


Fig. 1.—Photograph showing the deformity of the sternum.

frequently did not drink this quantity. He was 70 inches (178 cm.) tall and weighed 146 pounds (66 Kg.).

In March 1942 he was admitted to the Queen Elizabeth Hospital for further investigation, complaining of general weakness, pain in his muscles on exertion and pain in the back. Examination at the time showed an intelligent and well spoken man, cooperative, weighing 103 pounds (46.5 Kg.). The mouth was healthy; several teeth had been extracted. The spine was twisted, and movement appeared to be restricted in all directions, but examination was difficult. There was a deformity of the sternum, the manubrium sterni appearing to be in the normal position while the sternum itself was bent forward to give the appearance of an actual tumor (fig. 1). Impingement of the lower ribs on the iliac crests demonstrated the shortening of the spine. The remainder of the bony skeleton appeared to be of normal shape and to have no abnormal tumors. It was not tender to percussion in any area.

The skin was dry and scaly, and there were numerous erythematous areas, especially on the chest. The power in all groups of muscles was much greater

than might have been expected, but the patient was prevented from exerting his maximum strength by the pain that contraction caused. The greatest amount of pain seemed to arise during the phase of relaxation.

No clinical abnormality could be detected in the lungs, and it was impossible to make out the size of the heart owing to the gross deformities that were present. There was a harsh systolic murmur over the pulmonary area. The blood pressure was 115 systolic and 80 diastolic. The liver was not palpable. There was a semisolid rounded lump the size of an orange between the left costal

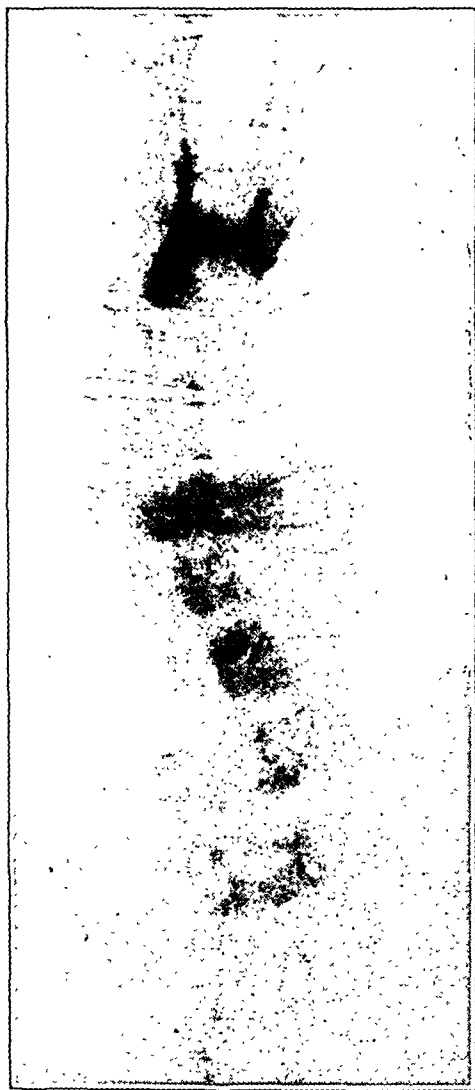


Fig. 2.—Thoracic and lumbar regions of the spine, showing osteoporosis and varying degrees of collapse.

margin and the iliac crest, which was tender on palpation. There was no alteration in reflexes, and no abnormality in sensation could be detected. The sphincters were normal.

The red blood cell count was 4,720,000 and the hemoglobin content 98 per cent. The white blood cells numbered 5,050 with 61.3 per cent polymorphonuclear cells, 1.0 per cent eosinophils, 26.7 per cent lymphocytes and 11.0 per cent monocytes. The urine contained no albumin, but there was inconstant glycosuria, while a urea clearance test showed a standard clearance of 54 cc. per minute, i. e., 96 per

cent of normal, in the first hour and 75 cc. per minute, i. e., 138 per cent of normal, in the second hour, with a blood urea content of 35 mg. per hundred cubic centimeters. A fractional test meal showed hyperacidity.

Initial analyses of the blood showed a plasma carbon dioxide-combining power of 55 volumes per cent, a plasma p_{H} of 7.32, a serum sodium chloride content of 600 mg., a calcium content of 10.3 mg. and a phosphorus content of 2.2 mg. per hundred cubic centimeters. The serum phosphatase level was 16.6 units (Jenner and Kay). The percentage of fat in dried feces was 19.8.

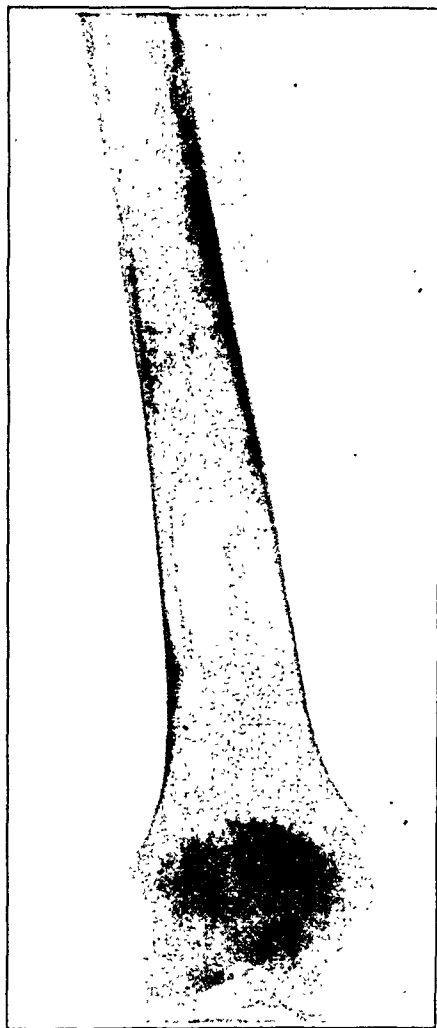


Fig. 3.—Right femur, showing osteoporosis, thinning of the cortex and preservation of normal striations of the bone.

Roentgenograms of the skull, humerus, spine, femurs and hands showed extensive osteoporosis; fractures of the ninth and tenth ribs were shown. There was no evidence of formation of cysts. The roentgenologic study was repeated after the patient had been two months on a diet containing 4 Gm. of calcium and 32,000 to 200,000 units of vitamin D daily. No change could be detected (figs. 2 and 4).

The details of investigations on calcium and phosphorus metabolism are given in table 1 and figure 5.

At the end of this period of observation, certain points were noted. With varying intake of calcium and large doses of vitamin D, the urinary excretion of calcium remained relatively low. The serum phosphorus content, contrary to the usual occurrence with vitamin D therapy, was depressed, while the urinary excretion of phosphorus was increased. Because of these findings, hyperparathyroidism appeared unlikely, and the absence of symptomatic improvement with vitamin D therapy and adequate diet was against a diagnosis of osteomalacia. A possibility remained that the patient's kidney was unable to reabsorb phosphate to allow of adequate levels of serum phosphorus. He was, therefore, discharged to await the development of suitable methods of investigation of this problem.

He was again admitted to the Queen Elizabeth Hospital on Aug. 20, 1943. His general condition was essentially unchanged, though roentgenograms sug-



Fig. 4.—Pelvis, showing osteoporosis, deformity of the pelvic brim and bilateral coxa valga.

gested that further decalcification had taken place. During the whole time he was in the hospital, glycosuria was present. A glucose tolerance test showed a fasting blood sugar content of 85 mg. and then 145, 140, 115 and 75 mg. per hundred cubic centimeters at subsequent half-hour intervals. Sugar was present in large amounts in the specimens taken after one and two hours. Examination of the urine showed no other abnormality and no cystine crystals. The initial examination of the blood showed a plasma carbon dioxide-combining power of 52.5 volumes per cent, a plasma pH of 7.20 and a plasma sodium chloride level of 573 mg. per hundred cubic centimeters. The serum albumin content was 5.0 Gm., the globulin content 2.9 Gm. and the serum calcium and phosphorus levels

9.5 and 0.8 mg. per hundred cubic centimeters; the serum phosphatase level was 20.9 units. A blood count showed 4,560,000 red blood cells, with a hemoglobin content of 90 per cent, and 7,300 white blood cells.

Further studies on excretion of calcium and phosphorus (tables 1 and 2) showed no essential changes from those carried out during the patient's first stay in the hospital.

Clearances of inulin and Diodone (the diethanolamine salt of 3,5-diiodo-4-pyridone-N-acetic acid) were studied on two occasions during the intravenous administration of inulin and Diodone¹ and on the third occasion after the serum level of phosphorus had been raised by infusion of 400 cc. of isotonic solution of phosphate.

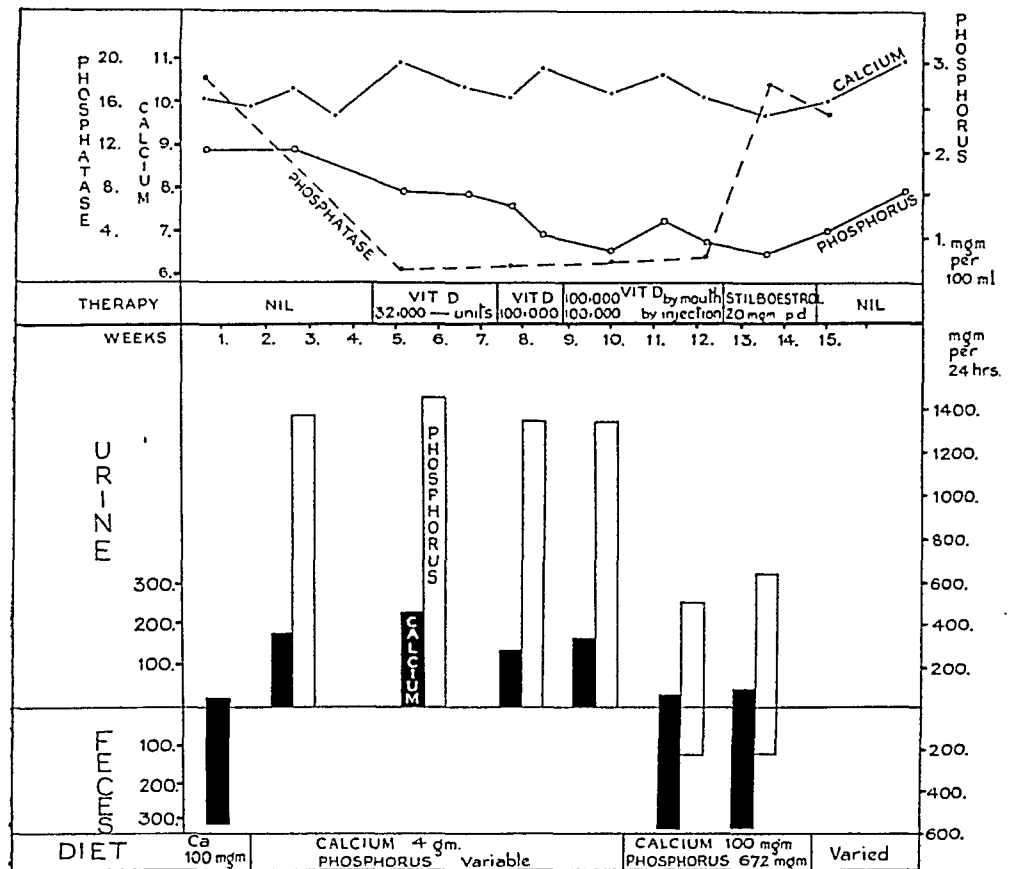


Fig. 5.—Chart showing the effects of diet and therapy on the calcium and phosphorus levels in the blood, urine and feces.

Clearance of inulin (eleven observations) averaged 93 cc. per minute (normal clearance, 90 to 120 cc.). The plasma clearance (ten observations, three experiments) averaged 522 cc. per minute and that in the blood flow 822 cc. per minute (normal for plasma but low for the blood flow, possibly due to overhydration causing a low hematocrit value).

The maximal rate of tubular excretion of Diodone was determined on one occasion, being 34 mg. per minute—a low normal value. Clearances of glucose

1. Smith, H. W.; Goldring, W., and Chasis, H.: Measurement of Tubular Excretory Mass, Effective Blood Flow and Filtration Rate in Normal Human Kidney, *J. Clin. Investigation* 17:263, 1938.

were determined in two experiments, from which the tubular excretion of glucose was calculated to be 112 mg. per minute (normal clearance, 200 to 300 mg. per minute). Clearance of phosphate was determined over seven periods, averaging 42 cc. per minute at a plasma level of 1.2 mg. of phosphorus (clearance of phosphate at normal plasma levels is 4 to 6 cc. per minute). In two periods, with the plasma level between 1.2 and 13 mg. of phosphorus, the clearance of phosphate exceeded that of inulin, viz., phosphate, 100 cc. per minute and inulin, 76 cc. per minute.

The interrelation between glucose and phosphorus levels in the blood was also followed.

Finally, the possibility that an acid urine might play some part in the poor absorption of phosphate was studied, and urine was collected under paraffin over twenty-four hours.

Random sampling on five separate days showed a varying p_H of 6.2, 5.8, 6.0, 5.2 and 5.6, the daily intake of fluid during the period of three weeks averaging 1,700 cc.

TABLE 1.—*Glucose and Phosphorus Levels in the Patient's Blood*

	Fasting	½ Hr.	1 Hr.	1½ Hr.	2 Hr.	2½ Hr.
Glucose.....	70	150	125	100	65	55 mg. per 100 cc.
Phosphorus.....	0.7	0.7	0.8	0.6	0.8	1 mg. per 100 cc.

TABLE 2.—*Results of Examination of Urine*

Specimen	Volume, Cc.	Hydrogen Ion Concentration	Ammonia, Total N/10 Acid
1.....	405	4.97	120
2.....	440	5.48	61
3.....	130	5.13	36.6
4.....	335	5.32	148
Total.....	1,310		365.6

Owing to the lack of beds at this point, it became necessary to transfer the patient back to the infirmary (Oct. 30, 1943). His condition remained stationary until June 1945, when symptoms of a peptic ulcer developed. On July 9, 1945 he had hematemesis. In spite of strict treatment for ulcer, his condition did not improve, and on August 28 he had further melena and showed signs of continued bleeding. Following transfusion, he improved slowly until October 7, when a further hematemesis proved fatal.

Gross Observations at Autopsy.—Owing to legal formalities, postmortem examination could not be carried out until four days after death, the body being kept in the refrigerator in the mortuary. The body was that of a pale man with deformity of both legs, kyphosis, scoliosis and lordosis of the spine, particularly in the thoracic region, and a definite bulging of the central portion of the center of the sternum.

The head appeared to be slightly increased in size. All bones were soft. The ribs showed reduction in the compact bone and could be distorted easily, the bone being extremely soft. The bodies of the vertebrae were similarly affected. A knife could be easily inserted into the substance of the bone.

There was a cystic swelling present in the left side of the loin.

Thorax.—The trachea and bronchi were normal. There were some adhesions between the right apex and the wall of the chest. This small area appeared to be a healed focus of tubercle. The lungs (weight, 1,008 mg.) were extremely edematous but were otherwise normal. The thyroid gland was normal in size. The parathyroid glands were normal (5 by 2 by 3 mm.), and the approximate total weight of four glands was 175 mg. The heart (weight, 448 Gm.) was enlarged, with hypertrophy of the right ventricle. The muscle was extremely pale, with thrush-breast mottling.

Abdomen.—The liver (weight, 1,288 Gm.) was pale. The spleen (weight, 72 Gm.) was normal in size and rather firm. The adrenal glands showed slight opacity in the medulla. Both kidneys (weight, 168 Gm. each) were extremely pale. The testes were small but were otherwise normal. The stomach was

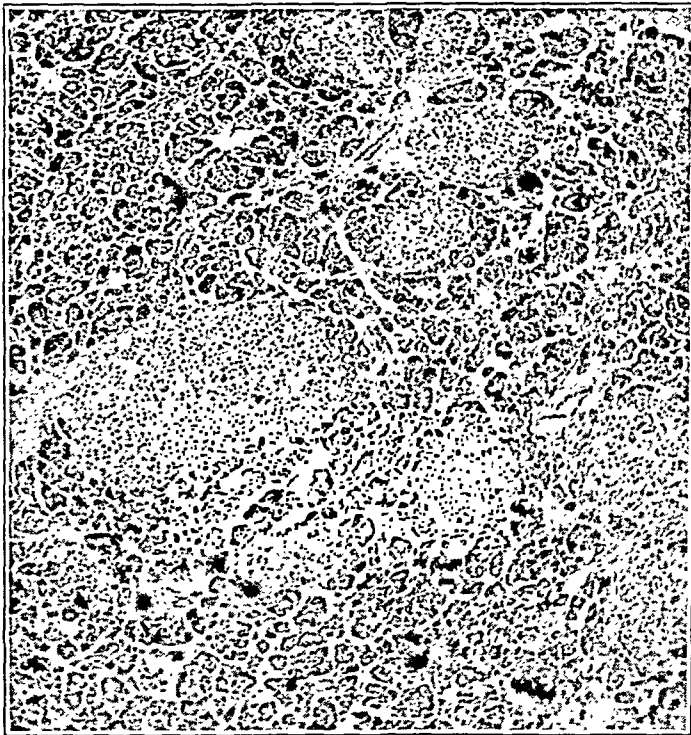


Fig. 6.—Representative section of the pancreas. Note the large amount of islet tissue. Stain, hematoxylin and eosin; $\times 60$.

slightly distended with altered blood. In the first part of the duodenum there was a large chronic ulcer eroding into the head of the pancreas. The pancreas appeared normal.

Head.—The brain (weight, 1,456 Gm.) showed slight edema. The vessels were healthy. The pituitary gland appeared to be normal. The bones of the skull were soft, but without undue thickening.

The swelling in the left side of the loin was between the internal oblique and transversalis muscles, and when incised it was cystic, with irregular walls, and appeared to be an old hematoma.

Histologic Examination.—Parathyroid Glands: The microscopic appearances of the parathyroids showed no evidence of hyperplasia (fig. 7).

Pancreas: The glandular portion of the pancreas appeared normal. The islets, however, were increased in number and size, comprising about one tenth of the field in sections taken from various parts of the organ and, in a few instances, as much as one third (fig. 6).

Adrenals, Pituitary, Testes, Thyroid Gland and Spleen: These showed no evident microscopic abnormality.

Liver: The lobules of the liver showed a coagulative necrosis of the central zone, and there was a slight polymorphonuclear reaction in the associated vessels. Widespread fatty change was present both in the central necrotic zones and in the outer zones. No trace of glycogen could be found in any part. A normal positive phosphatase reaction was given by the bile capillaries of the outer zones when tested by Gomori's method.

Kidneys: A generalized change was obvious in the epithelium of the first convoluted renal tubules. The lumens were full of granular debris. The cells showed pronounced vacuolation; in some the vacuoles were small, giving a

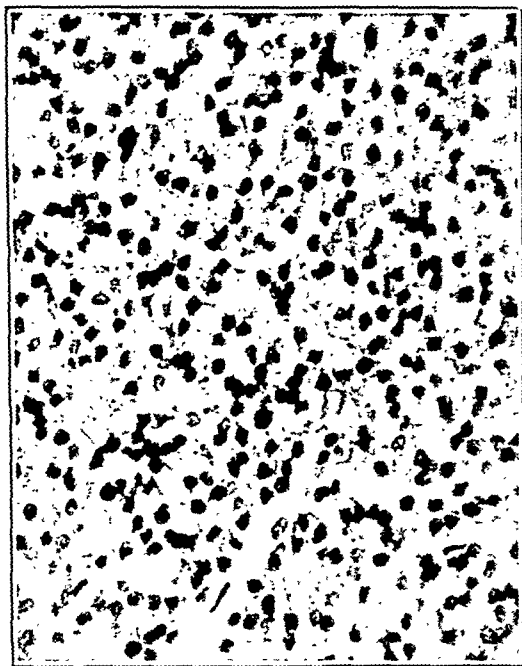


Fig. 7.—Section of the parathyroid gland. There is no sign of hyperplasia and none of the acinar formation or colloid secretion usually associated with hyperactivity. Stain, hematoxylin and eosin; $\times 320$.

foamy appearance to the cytoplasm, while in others the cytoplasm was reduced to a film covering a single large vacuole (fig. 8). In every tubule occasional necrotic cells could be found; in a few the whole epithelial lining appeared to have undergone necrosis, with pyknosis of nuclei. These changes were confined to the first convoluted tubules and were not generalized, as one might reasonably expect them to be if they had been due to postmortem change. Regeneration had occurred in parts, the epithelium being either in the form of basophilic cells with hyperchromatic nuclei or larger and frequently multinuclear basophilic masses with similar hyperchromatic nuclei. There was a general increase of connective tissue in the kidney, with thickening of basement membranes of both tubules and glomeruli, but foci of more decided fibrosis could be seen near glomeruli in relation to the second convoluted tubules (fig. 9) and at the junction of the cortex and medulla. Where fibrosis was present in the latter situation, the tubules had

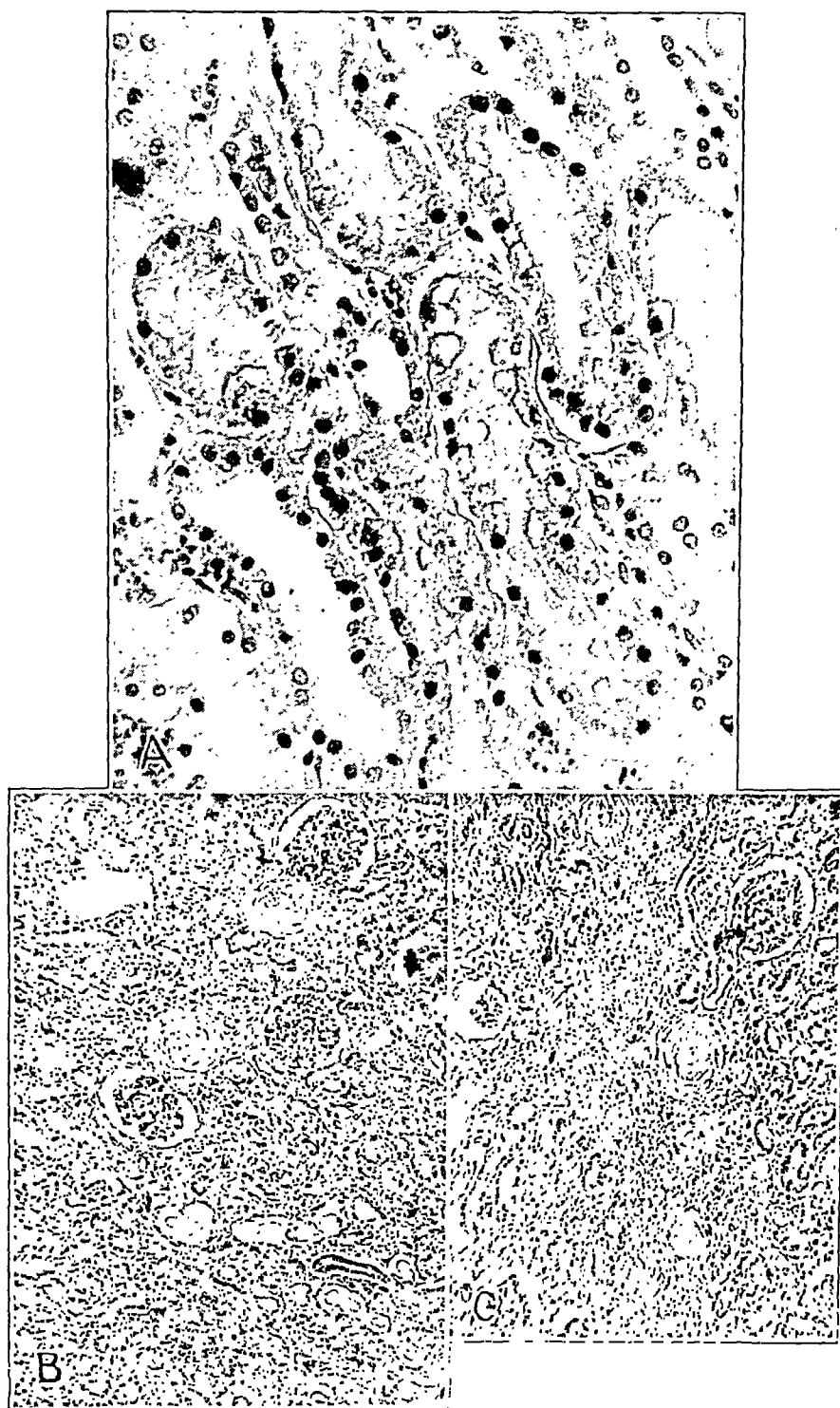


Fig. 8.—Photomicrographs of the kidney. Stain, hematoxylin and eosin. *A*, extreme vacuolation and degenerative changes in first convoluted tubules ($\times 320$). *B*, low power view of kidney showing focal fibrosis around second convoluted tubules ($\times 60$). *C*, section of kidney showing fibrous obliteration of ascending limbs of Henle ($\times 60$).

almost completely disappeared. In some cases the relative glomerulus had become hyalinized and the first convoluted tubule had undergone replacement fibrosis. A few colloidal casts were present in the ascending limbs of Henle. Staining with sudan dyes revealed a mild degree of fatty degeneration of the broad ascending limbs of Henle. The arteries showed some fibrosis of the media, but there was none of the arteriolar endarteritis usually associated with primary arteriosclerosis. Apart from the hyalinized glomeruli, the glomerular capillaries were normal.

Tests for sites of phosphatase activity revealed that this was practically absent. Only an occasional first convoluted tubule gave a faintly positive reaction.

Bone: Sections of bone from the femur showed a definite reduction in the thickness of the cortex; the subperiosteal layer was broken up into interlacing trabeculae resembling cancellous bone. At many points there were surface depressions containing dilated vessels, and the bone itself appeared to have lost a considerable amount of calcium. In a few places there were small masses of osteoid tissue

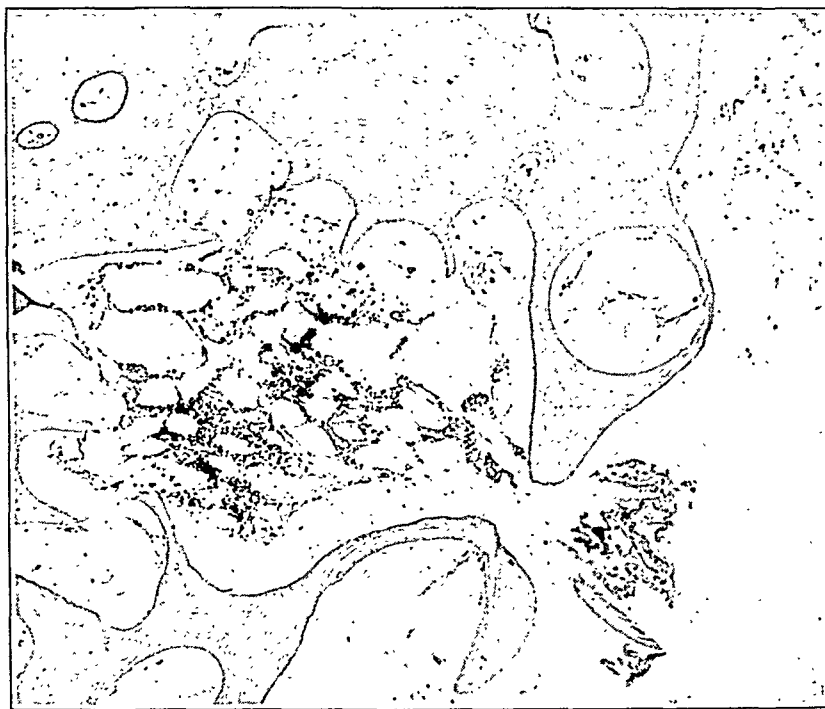


Fig. 9.—Section of bone showing thinning of trabeculae and increase in diameter of canals. Some loss of staining power at the edge of the bony trabeculae is just discernible. Stain, hematoxylin and eosin; $\times 60$.

and occasional osteoclasts, but the major change appeared to be a gradual atrophy. In the interior of the bone the trabeculae were much thinner than normal, staining bright pink instead of the normal basophilic color. This change was most noticeable at the edges of the trabeculae next to dilated vessels. No sign of activity of osteoclasts or of osteitis fibrosa could be seen in this part.

COMMENT

The presenting feature in this case was a slowly progressive osteoporosis. At first sight, the most logical explanation for this was the long and continued dietary deficiency in the years prior to the onset of the patient's symptoms, but the subsequent failure to respond to an

adequate diet and vitamin D rendered such a cause unlikely. Moreover, roentgenologically the bones had preserved their cancellous structure, a feature not usually noted in osteomalacia. Similarly, histologic examination of the various bones suggested only an extensive decalcification and not the excessive osteoid tissue of osteomalacia. Such a degree of osteoporosis may be seen in well defined conditions such as hyperparathyroidism, hyperthyroidism and chronic renal disease and in the persistent acidosis of certain cases of nephrocalcinosis,² in Fanconi's syndrome,³ and in steatorrhea. All of these, however, with the possible exception of hyperparathyroidism, were ruled out by the laboratory investigations. The persistently low urinary excretion of calcium in the presence of a normal plasma level made the diagnosis of hyperparathyroidism unlikely. Nevertheless, cases with low urinary excretion of calcium but high plasma values and others with high urinary excretion of calcium and normal plasma values have been reported,⁴ and in view of some similarities in the roentgenologic appearances of the bones of our patient the possibility, though remote, could not entirely be dismissed until the four normal parathyroid glands were demonstrated at autopsy.

The finding of a persistently low serum phosphorus content suggested a possible reason for the progressive decalcification. While a low serum inorganic phosphorus content in itself is not a bar to the laying down of bone in the presence of a relatively normal serum calcium level, it makes it probable that the concentration of more essential materials, such as phosphoric esters, are lacking to keep up the normal rate of deposition of bone.⁵ It was with the aim of raising the serum phosphorus level that massive doses of calciferol were given when the patient first came under observation; the subsequent fall was difficult to understand (fig. 5). If this case is analogous in any way to cases of refractory rickets,⁶ then it is possible that the dosage of vitamin D was insufficient both in duration and amount.

Any explanation of a low serum phosphorus level cannot be complete unless the role played by the kidney is considered. In our patient there was no disturbance of renal function as judged by standard tests, but

2. Albright, F.; Consolazio, W. V.; Coombs, F. S.; Sulkowitch, H. W., and Talbott, J. H.: *Metabolic Studies and Therapy in Case of Nephrocalcinosis with Rickets and Dwarfism*, Bull. Johns Hopkins Hosp. **66**:7, 1940.

3. Fanconi, G.: *Nondiabetic Glycosuria and Hyperglycemia in Older Children*, Jahrb. f. Kinderh. **133**:257, 1931.

4. Snapper, I.: *Medical Clinics on Bone Diseases: Text and Atlas*, New York, Interscience Publishers, Inc., 1943.

5. Robison, R.: *The Significance of Phosphoric Esters in Metabolism*, New York, New York University Press, 1932. Kay, H. D.: *Phosphatase in Growth and Disease of Bone*, Physiol. Rev. **12**:384, 1932.

6. Albright, F.; Butler, A. M., and Bloomberg, E.: *Rickets Resistant to Vitamin D Therapy*, Am. J. Dis. Child. **54**:529 (Sept.) 1937. Bakwin, H.; Bodansky, O., and Schorr, R.: *Refractory Rickets*, *ibid.* **59**:560 (March) 1940.

when the excretion of glucose and phosphorus were specifically considered it was clear that these functions of the kidney were abnormal.

With normal clearance of inulin and with a maximal tubular excretion of glucose of only 112 mg. per minute, glycosuria must exist at all normal levels of blood sugar. In our patient we were not able to determine whether the absence of sugar in the urine at certain periods was due to a phase of decreased rate of glomerular filtration or to a rise of the maximal tubular absorption of glucose since sugar was always present in the urine during the times we were carrying out our tests.

The daily excretion of phosphate and the studies of phosphate clearance suggested that the kidney was unable to handle phosphate normally. The defect might well be considered as poor reabsorption of phosphate alone, but the findings during the periods of raised serum phosphate content ruled out such a simple explanation. In this experiment, clearance of phosphate at raised plasma levels exceeded that of inulin, so that phosphate must therefore be secreted. In dogs, phosphate is secreted from plasma levels of about 6 mg. per hundred cubic centimeters, and there is inferential evidence that the same phenomenon occurs in human beings.⁷ Even so, the data in our case are insufficient to decide which factor is the more important, defective absorption or abnormal secretion.

The fact that autopsy could not be carried out until four days after death detracts from the value of the postmortem observations. Nevertheless, it was possible to demonstrate without normal parathyroid glands, some hypertrophy of the islets of Langerhans, abnormal thinning of the bony cortex and a large chronic duodenal ulcer. Some of the general changes in the liver and kidney were no doubt due to post-mortem autolysis, but this would not account for many of the focal changes in these organs, such as the central necrosis of the liver. Similarly, in the kidney, changes were confined almost entirely to the first and second convoluted tubules, and the fibrosis present was evidence of a long-standing condition. If such changes are accepted as having existed prior to death, then some pathologic evidence is offered in support of our hypothesis. It may be significant that the part of the nephron which showed extensive vacuolation and almost complete absence of phosphatase has been associated with reabsorption of phosphate.⁸ The distal nephron has been related to the reabsorption of sodium and acidification of the urine,⁹ and McFarlane¹⁰ has shown that

7. Barclay, J. A.; Cooke, W. T.; Kenney, R. A., and Nutt, M. E.: Phosphate Excretion in Man and Dog, read before the Physiological Society, 1946.

8. Smith, H.: *Physiology of Kidneys*, ed. 2, New York, Oxford University Press, 1943.

9. Pitts, R. F., and Alexander, R.: Renal Reabsorptive Mechanism for Inorganic Phosphate in Normal and Acidotic Dogs, *Am. J. Physiol.* **142**:648, 1944. Footnote 8.

10. McFarlane, D.: Experimental Phosphate Nephritis in Rat, *J. Path. & Bact.* **52**:17, 1941.

the excretion of excess acid phosphate will cause necrosis and resulting fibrosis in this area. Since large quantities of phosphate were being excreted in an acid urine, the epithelial degeneration and associated fibrosis in the distal tubules in our case may well be due to a similar mechanism.

There are insufficient data to do more than draw attention to the relationship between phosphate and glucose levels in the blood¹¹ and to suggest that the hypertrophy of the islets of Langerhans may have been a compensatory phenomenon.

SIMILAR CASES IN THE LITERATURE

Milkman¹² reported a case of a 40 year old woman whose condition he considered to represent a distinct clinical syndrome. She had suffered with progressive disorders of the bones over a period of eight years, the prominent features being lumbosacral pain, general weakness, difficulty in raising the legs to climb stairs, tenderness over the bones, especially those of the chest and pelvis, increased patellar reflexes and sclerotic changes in the bones resembling osteomalacia or late rickets. Roentgenograms revealed the presence of many transverse breaks or pseudo-fractures. The serum calcium varied between 15 and 10 mg. (more usually around 10 mg.) and the serum phosphorus between 2 and 6 or 8 mg. per hundred cubic centimeters (more usually around 2). There was also inconstant glycosuria, but no albuminuria. At autopsy "diffuse nephritis with arteriosclerotic changes" was noted. Sections from the left femur "did not resemble osteomalacia." All the involved osseous tissue showed strikingly increased vascularity; sections had to be cut with a saw except at the affected parts. The parathyroid glands were normal.

Michaëlis¹³ reported the case of an 18 year old youth with progressive softening of the bones. The serum calcium was within normal limits, but the serum phosphorus was low—1.8 to 2.0. A number of biopsies were made to exclude the possibility of the presence of myeloma, but the exact architecture of the bone was not studied in detail. Exploration revealed normal parathyroid glands. Vitamin D and a high calcium diet were totally ineffective.

11. McLeod, J. J. R.: *Carbohydrate Metabolism and Insulin*, London, Longmans, Green & Company, Ltd., 1926. Reiser, R.: Phosphorus Changes During Absorption of Oil and Glucose, *J. Biol. Chem.* **135**:303, 1940. Hanes, F. M., and Reiser, R.: Relation of Phosphorus to Fat and Glucose Metabolism in Sprue, *Am. J. M. Sc.* **200**:661, 1940. Kaplan, N. O., and Greenberg, D. M.: Action of Insulin on Phosphate Cycle, *J. Biol. Chem.* **156**:553, 1944.

12. Milkman, L. A.: Pseudofractures (Hunger Osteopathy, Late Rickets, Osteomalacia): Report of Case, *Am. J. Roentgenol.* **24**:29, 1930; Multiple Spontaneous Idiopathic Symmetrical Fractures. *ibid.* **32**:622, 1934.

13. Michaëlis, L.: Systemic Disease: Case, *Fortschr. a. d. Geb. d. Röntgenstrahlen* **45**:187, 1932.

Leedham-Green and Golding¹⁴ reported the case of a 34 year old woman with progressive deformity of the bones, multiple symmetric pseudofractures and diffuse osteoporosis. The serum calcium was 9.6 mg. and the serum phosphorus 2.2 to 2.8 mg. per hundred cubic centimeters, with a blood phosphatase value of 30 units. The authors discussed the question of terminology and proposed the use of the term osteoporosis melolytica or osteoporosis meloclastica.

Edeiken and Schneeberg¹⁵ made extensive observations on a 34 year old woman with numerous fractures. The disorder had arisen in childhood, and when first seen she was complaining of cramplike pains in the left thigh and of painful waddling gait. Roentgenographic examination showed fractures of both clavicles, the axillary border of the scapulas, the right radius and ulna, the left ulna, numerous ribs, both femurs, the right tibia and the left fifth and right third metatarsal bones. The serum calcium varied between 11.0 and 9.3 mg. and the phosphorus between 2 and 2.6 mg. per hundred cubic centimeters, and the phosphatase was slightly elevated. The urea clearance test showed a clearance of 73 per cent, with a blood urea content of 17 mg. per hundred cubic centimeters. Fishberg's concentration test showed specific gravities of 1,012, 1,011 and 1,012. The plasma carbon dioxide-combining power was 47 per cent and the serum chloride content 610 mg. per hundred cubic centimeters. The urine contained no albumin but showed intermittent glycosuria, without abnormal levels of sugar in the blood. The calcium balance test, with the patient on a 500 mg. intake of calcium, showed a slight negative balance and a low output of calcium in the urine.

The authors reviewed 19 other cases which they considered to be similar to their case. In all, the characteristic features were pain, disturbance of gait and the roentgenologic appearances of multiple transparent bands or pseudofractures, symmetrically located in various portions of the skeleton and usually interpreted as fractures. To cover this group of symptoms, they considered that the term "milkman's syndrome" should be retained until a definite etiologic agent was determined.

In all these cases the crucial point in the diagnosis has been the roentgenologic findings, in particular the presence of pseudofractures, and little attention has been paid to the biochemical features and the possible etiologic role of the kidneys. Camp and McCullough¹⁶ pointed

14. Leedham-Green, J. C., and Golding, F. C.: Osteoporosis Melolytica ("Multiple Spontaneous Idiopathic Symmetrical Fractures"), *Brit. J. Surg.* **25**: 77, 1937.

15. Edeiken, L., and Schneeberg, N. G.: Multiple Spontaneous Idiopathic Symmetrical Fractures: Milkman's Syndrome, *J. A. M. A.* **122**:865 (July 24) 1943.

16. Camp, J. D., and McCullough, J. A. I.: Pseudofractures in Diseases Affecting the Skeletal System, *Radiology* **36**:651, 1941.

out that pseudofractures are found in many diseases of the bones, and they listed more than fourteen conditions in which pseudofractures may occur; hence the mere presence of pseudofractures may be ruled out of discussion. In the cases reported by Garcin, Legrand and Bernard¹⁷ and Leriche and Jung,¹⁸ evidence is insufficient to establish their relationship to the case we are reporting. In others, the findings suggest other possible etiologic factors, such as hyperthyroidism,¹⁹ chronic renal disease²⁰ and osteomalacia.²¹ Lombard and Tillier²² reported the case of a 32 year old man, first seen by them at the age of 15. He was the fourth and only surviving son of a deformed mother. Osteotomies were performed at that time, when it was noted that the bones were excessively soft. The patient remained well and able to work and earn his living until the age of 32. At that time roentgenograms revealed the presence of forty-three pseudofractures. Chemical examination of the blood revealed a blood urea content of 53 mg., a cholesterol content of 278 mg., a calcium level of 9.6 mg. and a phosphorus level of 4.2 mg. per hundred cubic centimeters. This case had some features similar to those of our case, but the findings just prior to death suggested definite renal impairment similar to that in cases reported by Snapper.⁴

Fanconi,²³ in investigating a number of obscure metabolic upsets associated with resistant rickets in childhood, suggested that some might be associated with a functional defect of the renal tubules. He has reported a number of such cases associated with retention of chlorides and low phosphate content. McCune, Mason and Clarke²⁴ have reviewed these conditions, especially in respect to their occurrence in childhood.

17. Garcin, R.; Legrand, G., and Bernard, P.: Milkman Syndrome of Unknown Etiology: Clinical Cure and Roentgen Improvement Under Influence of Vitamin and Calcium Therapy, *Bull. et mém. Soc. méd. d. hôp. de Paris* **53**:1166, 1937.

18. Leriche, R., and Jung, A.: Spontaneous Nontraumatic Osseous Fissures of Undetermined Origin: Case, *Lyon chir.* **35**:47, 1938.

19. Guillaïn, G.; Lereboullet, J., and Auzépy, P.: Milkman Syndrome (Multiple Symmetrical Striae of Resorption): Nosographic Considerations; Case, *Bull. et mém. Soc. méd. d. hôp. de Paris* **53**:879, 1937.

20. Ravault, P. P.; Girard, M., and Didierlaurent: Symmetrical Spontaneous Fissuration (Milkman Syndrome), *Lyon méd.* **162**:189 and 217, 1938.

21. Debray, M.; Andre, T., and Gireaux: A Case of Multiple Spontaneous Fractures Difficult to Classify: Nosologic Discussion, *Bull. et mém. Soc. méd. d. hôp. de Paris* **49**:1038, 1933. Debray, M.: Chronic Painful Osteopathy with Multiple Symmetrical Pseudofractures: Case, *ibid.* **56**:573, 1940.

22. Lombard, P., and Tiller, H.: Spontaneous Fissuration of the Skeleton, *Mém. Acad. de chir.* **64**:336, 1938.

23. Fanconi, G.: Nephrotic-Glycosuric Dwarfism with Hypo-nephrotisch-glykosurische Zwergwuchs mit hypophospha-phosphatemic Rickets, *Jahrb. f. Kinderh.* **147**:299, 1936; footnote 3.

24. McCune, D. J.; Mason, H. H., and Clarke, H. T.: Intractable Hypophosphatemic Rickets with Renal Glycosuria and Acidosis (Fanconi Syndrome): Report of Case in Which Increased Urinary Organic Acids Were Detected and Identified with Review of Literature, *Am. J. Dis. Child.* **65**:81 (Jan.) 1943.

In 1935 Hunter²⁵ reported two cases essentially similar in detail to our case. The first was that of a 29 year old man who had suffered with repeated fractures of the superior ramus of the ischiatic bone, the left femur, the right ulna and the right tibia and right fibula, all being affected at various times. The serum calcium varied between 10.0 and 8.9 mg. and the serum phosphorus between 1.1 and 1.6 mg. per hundred cubic centimeters. The roentgenograms showed excessive decalcification of the bones. Renal glycosuria was constant.

The second case was that of a 35 year old man who presented severe and disabling pains in the bones, which had come on over a period of six months. The roentgenograms were similar to those in the first case. Renal glycosuria was also constant. The serum calcium varied between 10.3 and 11.5 mg. and the phosphorus between 0.4 and 1.3 mg. per hundred cubic centimeters. In both cases an exploration was made for parathyroid tumor, but none was found and the glands themselves appeared normal. Turnbull reported that sections of bone in the first case showed a great excess of osteoid tissue and moderately calcified bone. He considered that the diagnosis was osteoporosis and osteomalacia. Sections of bone in the second case showed no excess of osteoid tissue and considerable osteoporosis, but no evidence of osteitis fibrosa or osteomalacia. In both cases a decreased total output of calcium was noted, as well as an increase in the output of phosphorus in the urine. Hunter suggested that the kidneys failed to hold back phosphorus and calcium, just as they failed to hold back sugar, and that in consequence the plasma phosphorus content remained too low for normal formation of bone to take place.

It seems probable that in the cases reported by Michaëlis, Milkman, Leedham-Green and Golding, Hunter and Edeiken and Schneeberg the conditions were of similar origin, presenting as they did progressive softening of the bones, low serum phosphorus content, no evident renal disease and, in 4 cases, renal glycosuria. Therapy has so far failed to affect the condition.

Hunter's hypothesis that the kidney is at fault is supported by our findings. We would suggest, then, that there is a small group of cases in which osteoporosis is dependent on a defect of the renal tubules. The features of such a group are progressive softening of the bones, with or without fractures, unassociated with deficient dietary intake, signs of chronic nephritis or hyperparathyroidism, a normal serum calcium and a low serum phosphorus level, increased output of phosphorus and low excretion of calcium in the urine.

25. Hunter, D.: Studies in Calcium and Phosphorus Metabolism in Generalized Diseases of Bones, *Proc. Roy. Soc. Med.* **28**:1619, 1935.

The need, however, for further studies on excretion of phosphate in osteoporosis of obscure causation is evident. The low glucose threshold may or may not be part of the renal defect, but more cases must be studied before this question can be decided.

SUMMARY

In the case of a 39 year old man with progressive osteoporosis, laboratory and postmortem investigations suggested that a functional defect of the renal tubules led to a persistently low serum phosphorus content and that this was the cause of the osteoporosis. Six similar cases have been reported in the literature. Our case, in conjunction with these 6, offers support for Hunter's hypothesis that osteoporosis may on occasion be due to a renal defect unassociated with signs of chronic nephritis. The features of this group of cases are progressive osteoporosis, with or without fractures, unassociated with obvious dietary deficiencies, signs of chronic nephritis or hyperparathyroidism, in the presence of a normal serum calcium content, a low serum phosphorus content, an increased phosphorus level and a decreased calcium excretion in the urine, often associated with renal glycosuria.

Prof. W. H. Wynn gave us permission to investigate and publish the data on this case. Mr. Garfield Thomas, biochemist, and Mr. J. Parkes, assistant biochemist, Queen Elizabeth Hospital, and Miss J. Traught, biochemist to Dudley Road Hospital, made numerous biochemical investigations. Dr. J. F. Brailsford contributed advice on the interpretations of the roentgenograms, Dr. A. E. Chaplin carried out the postmortem examination and made the report and Dr. W. Whitelaw, pathologist to the Birmingham Municipal Hospitals, granted us permission to publish these data.

EARLY AMYLOID NEPHROSIS IN COMPLICATED TRAUMAS OF THE BONE SUSTAINED DURING WAR

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THE PROBLEM of the interrelation of the osseous and renal changes has long been known. More than twenty years prior to the writing of this paper, Barber¹ described a retardation of growth in children who have suffered for a long time from chronic nephritis or hydronephrotic atrophy of the kidneys. This retardation of growth may be associated with deformities of the bone and has been called "renal dwarfism" by the aforementioned author. Other authors use the terms renal infantilism, renal nanism or renal rickets for this disease (Shipley² and his co-workers, Lathrop,² Schoenthal and Burpee³ and others). Investigations of Parsons² indicate that in renal infantilism there is a considerably extended rarefaction of the bones, observed roentgenologically. Fishberg⁴ considered the term "renal rickets" a misnomer, as histologic osseous changes in this disease are much more closely related to those of hyperparathyroidism than to those of rickets. Moreover, his observations and those of Karelitz and Kolomozyeff⁵ and others would indicate that antirachitic therapy in these cases has little or no effect.

While the pathogenesis of the osseous changes in renal infantilism has not been altogether elucidated, Fishberg⁴ has stated the belief, however, that there can be little doubt that this osteodystrophy is the result of the disturbances in mineral metabolism, produced by renal insufficiency. Most probably this metabolic disturbance is closely connected with disturbances in calcium metabolism, as it was experimentally

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1. Barber, H.: The Bone Deformities of Renal Dwarfism, *Lancet* **1**:18 (Jan. 3) 1920.

2. Cited by Fishberg.⁴

3. Schoenthal, L., and Burpee, C.: Renal Rickets, *Am. J. Dis. Child.* **39**:517-528 (March) 1930.

4. Fishberg, A. M.: Hypertension and Nephritis, London, Baillière, Tindall & Cox, 1934.

5. Karelitz, S., and Kolomozyeff, H.: Renal Dwarfism and Rickets, *Am. J. Dis. Child.* **44**:542-555 (Sept.) 1932.

demonstrated by Pappenheimer,⁶ and is similar to the one present in primary parathyroid adenoma (Albright and others⁷ and Shelling and Remsen⁸). It appears evident that long-standing impairment of renal function leads to enlargement of the parathyroid apparatus.

Thus Pappenheimer and Wilens⁹ found that the weight of the parathyroids in patients with renal insufficiency averages more than 50 per cent greater than that of the parathyroids in controls. Highman and Hamilton¹⁰ demonstrated experimentally on rats that there is a hyperfunction of the parathyroid glands in chronic renal disease, as measured by the effect of a patient's blood on the calcium content of a rat's blood. Albright and his associates⁷ described similar alterations of the parathyroid apparatus in human beings with chronic nephritis. It is probable that the stimulus to the function of the parathyroids is retention of phosphate in renal insufficiency.

Rusakov,¹¹ one of the first in the Soviet literature to call attention to the interrelation existing between the kidneys and the osseous system, expressed the opinion that the osseous changes in renal insufficiency are seldom noticed only because they are not looked for. He suggested that every case of long-standing renal insufficiency entails hyperplasia of the parathyroid glands, with consequent development of the osseous changes of the type of osteodystrophy fibrosa, which he termed nephrotic osteopathies. He referred in these cases to the secondary hyperparathyroidism and not the primary one, i. e., Recklinghausen's disease. The latter is often associated with calcification of the renal parenchyma, with impairment of its function, or with the formation of calculi in the renal pelvis. Rusakov referred to the investigations of American authors who had found impairment of renal function with formation of calculi in 50 to 75 per cent of the instances of Recklinghausen's disease. He described 4 cases of parathyroid dystrophy, in 3 of which he observed changes in the renal parenchyma of the type of calcified metastasis, with impairment of its function, and in 1 the formation of calculi, with subsequent death of the patient.

6. Pappenheimer, A. M.: Effect of Experimental Reduction of Kidney Substance upon Parathyroid Glands and Skeletal Tissue, *J. Exper. Med.* **64**:965-980 (Dec.) 1936.

7. Albright, F.; Drake, T. G., and Sulkowitch, H. W.: Renal Osteitis Fibrosa Cystica, *Bull. Johns Hopkins Hosp.* **60**:377-399 (June) 1937.

8. Shelling, D. H., and Remsen, D.: Renal Rickets, *Bull. Johns Hopkins Hosp.* **57**:158-181 (Sept.) 1935.

9. Pappenheimer, A. M., and Wilens, S. L.: Enlargement of Parathyroid Glands in Renal Disease, *Am. J. Path.* **11**:73-91 (Jan.) 1935.

10. Highman, W. J., Jr., and Hamilton, B.: Hyperparathyroidism in Kidney Disease, *J. Clin. Investigation* **16**:103-105 (Jan.) 1937.

11. Rusakov, A. W.: Osteogenic Nephropathies and Nephrogenic Osteopathies, *Klin. med.* (no. 1) **17**:46-54, 1939; (no. 2-3) **17**:41-52, 1939.

As yet, however, it must be admitted that the pathogenesis of the formation of calculi is obscure, and there appears to be no reason for the belief that it is due only to the disturbances in calcium metabolism. Nevertheless, the investigations of a number of authors would indicate that the formation of stones in the kidneys is often observed in various neoplasms and inflammatory processes in bones, involving extensive destruction of bone and invasion of the blood by the products of altered calcium metabolism.

Moreover, if it is remembered that the disturbances in the vitamin balance of the organism, particularly a vitamin A deficiency (Gasparjan and Ovtchinnikov¹² and Osborne and Mandel¹³), as well as the changes in the equilibrium of the vegetative nervous system and the variations in the urinary and blood colloids also play an important role in the pathogenesis of the formation of stones, it will be easy to understand that the various injuries to the bone occurring under wartime conditions may lead to a comparatively rapid development of renal lithiasis. At the present time, similar conditions among the wounded participants of World War II have been already described. My associates and I have also observed 2 such cases of abundant formation of stones in kidneys, undoubtedly associated with injuries of bones sustained during the war.

In a discussion of the interrelation of the pathologic processes in the bones and in the kidneys it is necessary to mention also the myeloma, mostly a multiple osseous neoplasm described by Rustizky and Kahler and called therefore the Rustizky-Kahler disease. This disease favors the development in the bones of a neoplastic tissue of a specific character, followed by a considerable destruction of the osseous substance. Moreover, the urine and blood reveal the presence of albumose under the form of the so-called Bence Jones protein. Numerous original hyaline casts are to be found in the kidneys, giving an intensive color reaction of amyloid with the use of congo red. As a matter of fact, this last circumstance gave some authors the ground to speak of a chemical relationship between amyloid and the Bence Jones albumose.

Rustizky-Kahler disease may lead to a complete occlusion of the nephrons by the Bence Jones albumose and consequently to oliguria and anuria, to the onset of renal insufficiency and finally to uremia. While edema is a common feature of the cachectic condition in patients with other malignant neoplasms, it is characteristic, according to Fishberg⁴ and other authors, that in this form of neoplasm it is not observed.

12. Gasparjan, A., and Ovtchinnikov, N.: Zur Frage der Steinbildung im Organismus (Avitaminose und Steinbildung), *Ztschr. f. urol. Chir.* **30**:365-374, 1930.

13. Cited by Volhard, F., and Suter, F.: Nieren und ableitende Harnwege, in Mohr, L., and Staehelin, R.: *Handbuch der inneren Medizin*, Berlin, Julius Springer, 1931, vol. 6, pt. 2, p. 1913.

Rusakov¹¹ considered that the Bence Jones albumose is the result of the impairment of the intraosseous intercellular protein metabolism and called the entire process in the kidneys osteogenous nephropathy.

There exists, however, still another, more intimate, relationship between the osseous system and the kidneys, a relationship in which the kidneys act as a conjugate but unique organ and as a system connected by the community of humoral and nervous relations with the whole organism. I refer to amyloid nephrosis, a disease whose position in the scheme of the classification of renal diseases offers some difficulties. From the purely morphologic standpoint, the amyloid kidney is, perhaps, most closely related to arteriosclerotic diseases of the kidneys, for the lesions are primarily degenerative changes in the renal vessels. But, clinically, except in unusual instances of amyloid contracted kidney, the principal features of the disease seem to consist in the degenerative changes in the tubular epithelium of the kidneys and not in the circulatory changes in the glomeruli.

It is still considered an established fact that amyloid nephrosis is closely associated pathogenetically with the presence of long-standing chronic diseases accompanied with cachexia and, more particularly, with pulmonary and osteoarthritic tuberculosis and long-standing suppurations, such as those in empyema, bronchiectasis, pulmonary abscess, osteomyelitis and other conditions. However, the question of the necessity in the presence of a long-standing suppurative or infectious process for the development of amyloid nephrosis requires reconsideration. A series of findings of older authors have been recorded who have proved experimentally the possibility of an extremely early development of amyloidosis and amyloid nephrosis. Thus Krawkow in 1896 found amyloid after eleven days of experimentally produced suppuration in rabbits.

Birch-Hirschfeld in 1892 observed the development of amyloidosis under similar conditions within six weeks. An American investigator, Dickinson, found amyloidosis in a patient three weeks after a compound fracture, and Rosenblatt,¹⁴ also an American, observed the development of amyloidosis among one fifth of his tuberculous patients within less than two years from the onset of tuberculosis and in some patients even within not later than six months thereafter. Lichtwitz¹⁵ described a case of the development of amyloid nephrosis and amyloidosis of the spleen in a patient who died of pneumonia within three weeks.

These facts are not only of diagnostic but also of prognostic importance. Usually in patients in the early stages of the disease amyloid

14. Rosenblatt, M. B.: Recovery from Generalized Amyloidosis Secondary to Pulmonary Tuberculosis, *Arch. Int. Med.* **57**:562-565 (March) 1936.

15. Lichtwitz, L.: *Die Praxis der Nierenkrankheiten*, Berlin, Julius Springer, 1925.

nephrosis often figures in the hospitals under the diagnosis of "decompensation of cardiac function" or "nephronephritis" and in the later stages, with the onset of renal insufficiency, as chronic nephritis. Naturally this may lead to defective treatment. On the other hand, a vigorous treatment effectively pursued to combat the basic pathogenetic source of the disease may not only save the patient from premature death but lead to full recovery in cases in which the process in the kidneys is not yet in the incurable stage. A number of cures thus attained have been reported (Waldenström,¹⁶ Fishberg,⁴ Reimann¹⁷ and others) which took place once the primary cause of amyloid nephrosis had been removed. We have also seen such an instance of complete recovery from amyloid nephrosis (at least the clinical course did not reveal the presence of amyloid during a two year period) in a patient with tuberculous osteomyelitis of the hip after the amputation of the extremity. That amyloidosis can regress once the cause has been removed is known also from the experiments of Kuczynski¹⁸ in 1922.

Because of the view that amyloid nephrosis requires a prolonged period for its development, this disease may not be always recognized in time, and the possibility of its effective treatment may thus be neglected.

Moreover, amyloid nephrosis is often not recognized because of the erroneous view that this process is accompanied usually with pronounced albuminuria, as in chronic and lipid nephrosis.

Despite this extended point of view, it should be borne in mind that albuminuria in the presence of amyloid nephrosis is variable and at times may practically disappear. The number of formed elements present in the urinary sediment in amyloid nephrosis is extremely low, much lower than that in equally severe albuminuria in other forms of renal disease.

Edema is an exceedingly common symptom of amyloid nephrosis, and as a rule the lower extremities are first and most affected. The latter fact presents another occasion to attribute the origin of edema to the presence of a nonexisting or hardly onsetting cardiac weakness. Ascites is not uncommon, and sometimes there may be ascites in the absence of anasarca. Hydrothorax is extremely rare.

If it is further added that in amyloid nephrosis diarrhea may be present as an evidence of intestinal amyloidosis, it will be easy to

16. Waldenström, H.: Formation and Disappearance of Amyloid in Man, *Acta chir. Scādinav.* **63**:479-530, 1928.

17. Reimann, H. A.: Recovery from Amyloidosis, *J. A. M. A.* **104**:1070-1071 (March 30) 1935.

18. Kuczynski, M. H.: Neue Beiträge zur Lehre vom Amyloid, *Klin. Wchnschr.* **2**:727-730, 1923.

understand why these patients are often treated for avitaminosis, chronic enterocolitis, dysentery or alimentary dystrophy.

It would seem that an accurate analysis of the diagnostic particularities in amyloid nephrosis will show that its frequency among wounded patients with complicated traumas of the bone sustained during the war may be much higher than it is supposed. At least after special attention had been called to this problem we had the occasion to observe several such patients.

As an illustration short summaries of cases of some of such patients are submitted.

REPORT OF CASES

CASE 1.—D. E., a private aged 33, was wounded on Aug. 1, 1942 by a mine fragment in the left humerus. He was admitted to the evacuating hospital with a plaster cast applied, which was left undisturbed. Pronounced edema of the lower extremities and the face was present. Urinalysis (made first on August 22) revealed up to 3 Gm. of albumin per hundred cubic centimeters, 2 or 3 hyaline casts in the sediment and 3 to 5 alkalized red blood cells microscopically. There was diarrhea without mucous or bloody stools. The patient died on August 26 with symptoms of cardiac insufficiency.

Clinical Diagnosis.—There was a gunshot fracture of the left humeral bone, with a suppurative process, and wounds involving the soft tissue of the left thigh. Nephritis (with possibly a renal abscess) and colitis were present.

Autopsy.—Autopsy was performed on August 27. The spleen was sharply enlarged (weight 500 Gm.), extremely hard and of elastic consistency, and it broke on section. On scraping, pulp was absent. The kidneys were enlarged, weighing together 525 Gm., and had a hard surface; the tissue appeared sharply pale, waxy and hard and was marked by the appearance of slightly yellowish spots on the surface. Application of strong solution of iodine, U. S. P., produced brownish small dots and strips (a reaction positive for amyloid). The mucosa of the pelvis, ureter and urinary bladder was pale.

Anatomic Diagnosis.—A gunshot fracture, by fragment, of the left humeral bone, with consequent osteomyelitis and suppuration of the soft tissues in the region of the fracture, was present. There were two fistulous communications in the skin of the left humerus in the region of the wound. Also found were amyloid nephrosis, amyloidosis of the spleen (which was lardaceous) and fresh serofibrinous ascitic peritonitis.

This was a case of sharply pronounced amyloid nephritis which developed within two or three weeks after a gunshot wound, with consequent osteomyelitis. The most careful research during autopsy did not reveal any other cause for the development of the disease.

CASE 2.—I. D., a private aged 40, was wounded on Feb. 23, 1942 in the region of the left knee joint. Arthrotomy was performed on March 6. During the course of the operation there was a copious discharge of pus. On March 25 the patient was evacuated to the base hospital, with complaints of great pains in the left leg. The discharge of pus from the wound was still copious. On April 14 edema made its appearance, occurring first in the lower extremities and then in the whole body. Beginning on April 23 the patient had frequent watery stools. On May 4 the possibility of amyloid nephrosis was first suspected. The urine

contained from 1 to 6 Gm. and more of albumin per hundred cubic centimeters and a few formed elements in the sediment. The patient showed growing general weakness, and he died on April 15 in the last degree of cachexia.

Autopsy.—Autopsy revealed osteomyelitis of the left femur, amyloid nephrosis and amyloidosis of the spleen, liver and bowel.

In this case, as in the previous one, besides osteomyelitis, autopsy did not reveal any other cause for the development of amyloid nephrosis. The disease developed probably within six or seven weeks after the injury. Possibly an early radical operation could have saved the patient.

CASE 3.—Y. K., a private aged 27, sustained an incomplete wound by shell fragment in the region of the third thoracic vertebra on June 11, 1942. There were signs of compression of the spinal cord. On June 13 laminectomy was performed, with the application of a fixating splint. From July 30 there appeared small bed sores, measuring 2 by 1 and 3 by 1 cm., in the region of both trochanters. These increased and extended, and there appeared a copious purulent discharge. On July 20 the patient was evacuated to the base hospital. On July 27 there was 0.66 Gm. of albumin per hundred cubic centimeters in the urine, with no formed elements; later the albumin disappeared from the urine. On August 20—two months and nine days after injury—edema of the feet and then of the whole body appeared. From August 28 there was diarrhea, with growing cachexia. Albumin was present, from 0.33 to 1.65 Gm. per hundred cubic centimeters; no casts were seen. The patient died on September 15 with pronounced cachexia.

Clinical Diagnosis.—An incomplete wound of the spinal column in the region of the third thoracic vertebra was seen. There were also paraplegia of the lower extremities, paralysis of the pelvic organs, amyloid nephrosis and bed sores.

Autopsy.—Autopsy performed on September 7, revealed the liver to be large and hard, with a greasy luster. The kidneys were large and white. There was a positive reaction to strong solution of iodine, U. S. P. At the level of the fourth and fifth thoracic vertebrae there was an opening through the spine and ribs into the right pleural space.

Diagnosis.—The diagnosis of an incomplete wound of the spine, with consequent myelitis was made. There were purulent pleurisy and pneumonia, with an abscess, involving the left side. There was also amyloidosis of the internal organs along with amyloid nephrosis.

In this case amyloidosis developed within three months after the patient's injury. The possible causative factor seems not to be trauma of the bone directly but processes associated with this condition (purulent pleurisy involving the left side, abscess of the lung and bed sores).

CASE 4.—I. M., a private aged 32, was wounded on June 13 by mine fragments in the lumbar region, both buttocks and feet. It was recorded on July 4 in the front hospital that he had a wound measuring 3 by 1 cm. in the region of the "lumbar vertebrae," with copious purulent discharge. On July 8, less than one month after injury, the patient, because of general edema and poor general condition and the presence of up to 6 Gm. of albumin per hundred cubic centimeters of urine, was evacuated to the base therapeutic hospital. On July 9 the blood pressure was 110 systolic and 55 diastolic. Albumin in the urine varied from 2.31 and 2.64 to 4.29 Gm. per hundred cubic centimeters. A small quantity of hyaline casts was present in the sediment. On July 17 the patient looked

extremely pale and weak and there was considerable edema of the lower extremities and the scrotum. From August 4 there were diarrhea and cachexia. The patient died on August 12.

Clinical Diagnosis.—Osteomyelitis of the right iliac bone was diagnosed, with nephritis and enterocolitis.

Autopsy.—At autopsy the kidneys were enlarged, hard and light yellow. The spleen was hard and lardaceous.

Anatomic Diagnosis.—The anatomic diagnosis was osteomyelitis of the left iliac bone after a gunshot wound, with amyloid nephrosis and amyloidosis of the spleen and bowel.

CASE 5.—I. M., a private aged 36, was wounded on Feb. 12, 1942 by a mine fragment in the left thigh. On February 16 there was a copious discharge of pus from the wound. The patient was recorded as having osteomyelitis of the left femoral bone. On April 22, two months and ten days after injury, the onset of general edema occurred. The blood pressure was 105 systolic and 70 diastolic. Urinalysis revealed 0.33 Gm. of albumin per hundred cubic centimeters and hyaline casts in the sediment.

Diagnosis.—Avitaminosis was diagnosed. In spite of an adequate diet the edema lasted. Purulent discharge from the wound continued. In the urine there were varied amounts of albumin—from 0.33 to 1.28 Gm. per hundred cubic centimeters. The blood pressure was not high. On May 25 amputation was performed through the lower end of the left femur. On June 16 diarrhea developed; the edema diminished. The patient died on June 22.

Clinical Diagnosis.—The clinical diagnosis was amputation of the left femur due to traumatic osteomyelitis, with amyloid nephrosis.

Autopsy.—Autopsy was performed on June 23. The kidneys were enlarged, weighing together 582 Gm., and of hard consistency, revealing a light yellow, waxy tissue. There was a positive reaction to strong solution of iodine, U.S.P. The spleen was hard, fragile and lardaceous.

Anatomic Diagnosis.—The anatomic diagnosis was amyloid nephrosis, with amyloidosis of the spleen.

As seen from the foregoing report, in this case the amyloid nephrosis developed within four months after injury. The amputation of the wounded extremity, executed three and a half months thereafter, did not stop the progress of amyloidosis, probably being too delayed.

We have at our disposal 28 such cases as described here in which the diagnosis of early amyloid nephrosis and amyloidosis of various internal organs (spleen, liver or bowel) was established during autopsy (or partially clinically). All of them are more or less similar as to the course of the disease. We observed some patients who had early amyloid nephrosis which developed in direct connection with the complication of trauma of the bone sustained in the war but in whom the process was considerably less acute. Owing to the improvement in the basic traumatic process, all the patients were discharged from hospitals in a more or less satisfactory condition. However, the osteomyelitic process, as well as the process in the kidneys, is probably only in an inactive stage. For these reasons, the possibility of further

progress of amyloidosis and amyloid nephrosis resulting in the amyloid contracted kidney, with all its severe consequences, is always awaiting these patients. To our regret, due to present conditions, further observation of these patients is rather complicated.

In view of the fact that the diagnosis of amyloid nephrosis, especially in its early stages, presents some difficulties and may always provoke some doubt, especially if it is not confirmed by the Bennhold reaction with the solution of congo red (which test we could not use because of technical circumstances), I have described only the cases in which the diagnosis was confirmed by autopsy. Evidence has been accumulated which indicates that often cases of amyloid nephrosis have been recorded in which not only clinically but even at necropsy it was impossible to establish the primary cause for the development of the process. The suppurative process may be so insignificant and so deeply hidden in various tissues that it may easily escape the attention of the prosecutor even during the most careful search. Probably in our cases too the cause for the development of the amyloid process was not the complicated trauma suffered in the war but some other long-standing infectious suppurative process which was present in the organism of the patients long before the trauma.

It would appear, however, that such an admission is extremely artificial. It is hardly admissible that all our patients could have such a long-standing process without its being revealed clinically or at necropsy. Perhaps such a supposition is apt to be true in regard to some of our patients, but it cannot be extended to include all of them. Too clear in our cases is the association of the process with the trauma, and too often was there a development of both processes to deny their relationship.

Unexpected and totally inconsistent with our usual observations is the extremely early development of amyloid nephrosis which occurred after the trauma in our cases. Thus in our first case the amyloid nephrosis developed within two or three weeks after the injury and in the other cases within two or three months. The latter term, sufficiently early too in comparison with the usual occurrence in our cases, we observed in the case of a wounded soldier, in whom proved amyloid nephrosis developed eight months after the injury.

However unexpected this fact may be, it must not astonish physicians. Conditions in wartime may cause exceedingly original courses and highly varied pictures of the usual and well known pathologic changes. This does not refer only to the problem which is of interest to us but to the varied pathologic pictures, the original forms of which, under the conditions occurring in wartime, every more or less observing clinician may note at the present time. Malaria, pneumonia, pneumosclerosis and other related conditions assume at the present time

such original forms that their diagnosis offers some difficulties. In particular, in connection with the renal pathologic changes, the so-called war (trench) nephritis is worthy of mention. Its course differs so considerably from the acute diffuse nephritis occurring in peacetime that a number of authors have been inclined to consider it a special nosologic variety, even though it does not differ either pathogenetically or clinically from the latter. It is easy to assume, therefore, that in the organism exposed for a long time to the hardships of life in the open air, frequent cold (and perhaps light infections), altered diet and strong psychic trauma the process of the development of amyloid nephrosis may progress more swiftly.

Such conditions as described here are rather rare; however, they are more frequent than it may be supposed. The interest in them is not only of a theoretic character, consisting in the mere possibility of such an early development of amyloid nephrosis. A timely diagnosis of such impairments of renal function in wounded persons should call for greater activity on the part of surgeons, including more energetic and radical surgical intervention. This in its turn may be lifesaving in such cases or may preserve the patients from early painful invaliding and finally from premature death.

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EXCRETION OF UROBILINOGEN IN THE URINE IN INFECTIOUS HEPATITIS

Serial Studies

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ALTHOUGH it has been known for many years that the Ehrlich reaction for urobilinogen in the urine and feces is a sensitive test of hepatic dysfunction,¹ not until recently has there been a simple quantitative method for its determination. In 1944 Watson and others described a simple quantitative method for measuring the urinary excretion of urobilinogen.

During the active phases of the Pacific campaign, in a hospital in Guadalcanal, we had the opportunity of comparing this test with several other sensitive tests of hepatic function in the study of 120 cases of infectious hepatitis. We attempted to determine whether or not this test could be used in assisting clinical judgment to decide when convalescence should be terminated. Most of our patients were seen after jaundice had developed and were followed during the period of convalescence to complete recovery or to the point at which it was evident that their convalescence would be considerably prolonged and that the need for further rest required their evacuation to the zone of the interior.

One of the main purposes of tests of hepatic function in cases of hepatitis is to determine when convalescence has progressed far enough so that there is the minimum possibility of relapse after a patient has resumed his daily activities. Certain tests of hepatic function are important also in the estimation of residual hepatic damage many months after the acute disease has subsided. They may also be used in group survey studies during an epidemic of infectious hepatitis to detect patients who are without icterus but who do have latent disease. Such studies may reveal subclinical forms of disease, which, if undiscovered, might progress and leave permanent hepatic damage.²

From the Department of Medicine, Northwestern University Medical School.

Read before the Midwest Section, American Federation for Clinical Research, Chicago, Oct. 31, 1946.

1. Wallace, G. B., and Diamond, J. S.: Significance of Urobilinogen of the Urine as a Test of Liver Function, *Arch. Int. Med.* **35**:698-725 (June) 1925.

2. Hallock, P., and Head, D. P.: Simple Laboratory Test as Aid in Recognizing Early Hepatitis, *Bull. U. S. Army M. Dept.* **5**:236-242 (Feb.) 1946.

As long as the patient with acute infectious hepatitis is jaundiced and has a palpable, tender liver, there is no question of his status as a bed patient or of the deficiency of his hepatic function. Therefore, gross tests of hepatic function, such as dextrose and galactose tolerance tests and tests for hippuric acid synthesis and abnormal cholesterol levels, which may reveal abnormality during the acute phase, usually are not helpful in the ultimate management of the patient. Abnormalities in the alkaline serum phosphatase activity and in the amount of cholesterol esters, total protein and globulin in the plasma have their greatest prognostic value early in the course of the illness and are much less important late in convalescence or in chronic hepatitis. More sensitive tests of hepatic function, such as Hanger's cephalin-cholesterol flocculation test, the thymol turbidity test, the one minute direct van den Bergh reaction and the thirty minute sulfobromophthalein excretion test, have been fairly reliable guides to recovery.³ On many occasions, however, relapses have occurred after the reactions to these tests have become normal and after the patient has apparently recovered clinically, in some instances having been ambulatory for seven to ten days or longer. Thus a test which may aid in the detection of latent or incompletely cured hepatitis is greatly desired. To this end, the two hour quantitative excretion of urobilinogen has been observed during the convalescence of 120 patients with infectious hepatitis.

METHOD

The technic of the Watson test for urobilinogen in the urine depends on the comparison of the color developed in the urine by the Ehrlich diazo reagent with that developed by a stock solution of a standard dye (pontacyl fast pink, E. K.).⁴ Estimations can be made in a simple comparator block or in the Evelyn or some other photoelectric colorimeter. In normal circumstances the maximum rate of excretion of urobilinogen occurs between 2 and 4 in the afternoon and probably does not exceed a total of 1.0 to 1.5 Ehrlich units for the two hour collection period. The usual normal range in our experience varied from 0.6 to 0.8 unit for the two hour period. In hepatic dysfunction of the sort caused by infectious hepatitis but without complete biliary obstruction, more than 1.0 Ehrlich unit is excreted during this same period. The normal urinary excretion in twenty-four hours is usually less than 5.0 Ehrlich units.

3. Barker, M. H., and Capps, R. H.: Acute Infectious Hepatitis in the Mediterranean Theater Including Acute Hepatitis Without Jaundice, *J. A. M. A.* **128**:997-1003 (Aug. 4) 1945. Barker, M. H., and Capps, R. H.: Chronic Infectious Hepatitis in the Mediterranean Theater, *J. A. M. A.* **129**:653-659 (Nov. 3) 1945.

4. Schwartz, S.; Sborov, V., and Watson, C. J.: The Quantitative Determination of Urobilinogen by Means of the Evelyn Photometer Colorimeter, *Am. J. Clin. Path.* **14**:598-603 (Dec.) 1944. Watson, C. J.; Schwartz, S.; Sborov, V., and Bertie, E.: A Simple Method for Quantitative Recording of the Ehrlich Reaction as Carried Out with Urine and Feces, *Am. J. Clin. Path.* **14**:605-615 (Dec.) 1944.

During the course of this study on hospitalized patients with infectious hepatitis, we made a control series of urobilinogen excretion tests on a comparable group of young men, who were hospitalized in the surgical wards of the hospital. The test was performed between 2 and 4 p. m. on 56 patients. In 52 patients the results were normal. Four had excretions of urobilinogen in the urine of over 1.0 Ehrlich unit in two hours. The values were 1.2, 1.4, 1.45 and 1.5 Ehrlich units respectively. We did not have an opportunity to perform serial studies or other tests of hepatic function on these patients. In the 52 cases in which the values were less than 1.0 Ehrlich unit, the results ranged from 0.4 to 0.8 unit. Five patients with acute malaria and enlargement of the liver were tested. They excreted normal amounts of urobilinogen in the urine during the first five days of the disease, whereas 3 patients with amebic hepatitis had excretion values of more than 5.0 Ehrlich units in a two hour period. Studies of the twenty-four hour excretion of urobilinogen in the urine were performed on 5 normal controls. All 5 excreted less than 5.0 Ehrlich units in twenty-four hours.

RESULTS

The results of our studies will be presented in two parts: first, a report of the usefulness of serial determinations of the two hour excretion of urobilinogen in the urine in the management of patients with infectious hepatitis; second, a comparison of this test with other standard tests of hepatic function in a group of patients with acute infectious hepatitis. Even though our purpose in this present study was to compare the Watson two hour test of urobilinogen excretion with other tests, we are fully cognizant of the fact that no single estimation of hepatic function will measure over-all hepatic damage and that an evaluation of many tests is necessary. It is important that serial tests of hepatic function be done during the course of an acute infectious process of the liver. This was found to be particularly true of the Watson two hour test.

Part 1.—Tests for excretion of urobilinogen in the urine were done on each patient with infectious hepatitis at least every other day during the convalescent period, and not until three to five normal values were obtained over a seven to ten day period was convalescence considered to be completed. In doing serial studies, we noted that during the course of the illness and particularly during the convalescent period there were wide fluctuations in the amount of urobilinogen excreted in the urine and that unless the tests were performed at least every other day and interpreted for the individual patient the occasional test or spot check might give misleading normal values. Often these values were normal during the first two or three weeks of illness, until the icteric index reached the maximum level, becoming abnormal only after the icteric index began to decline (fig. 1 *A* and *B*). During convalescence there would be wide fluctuation, until the patient recovered, at which time the excretion of urobilinogen in the urine leveled off at normal values (fig. 1 *C*). On other occasions there would be a rather close correlation

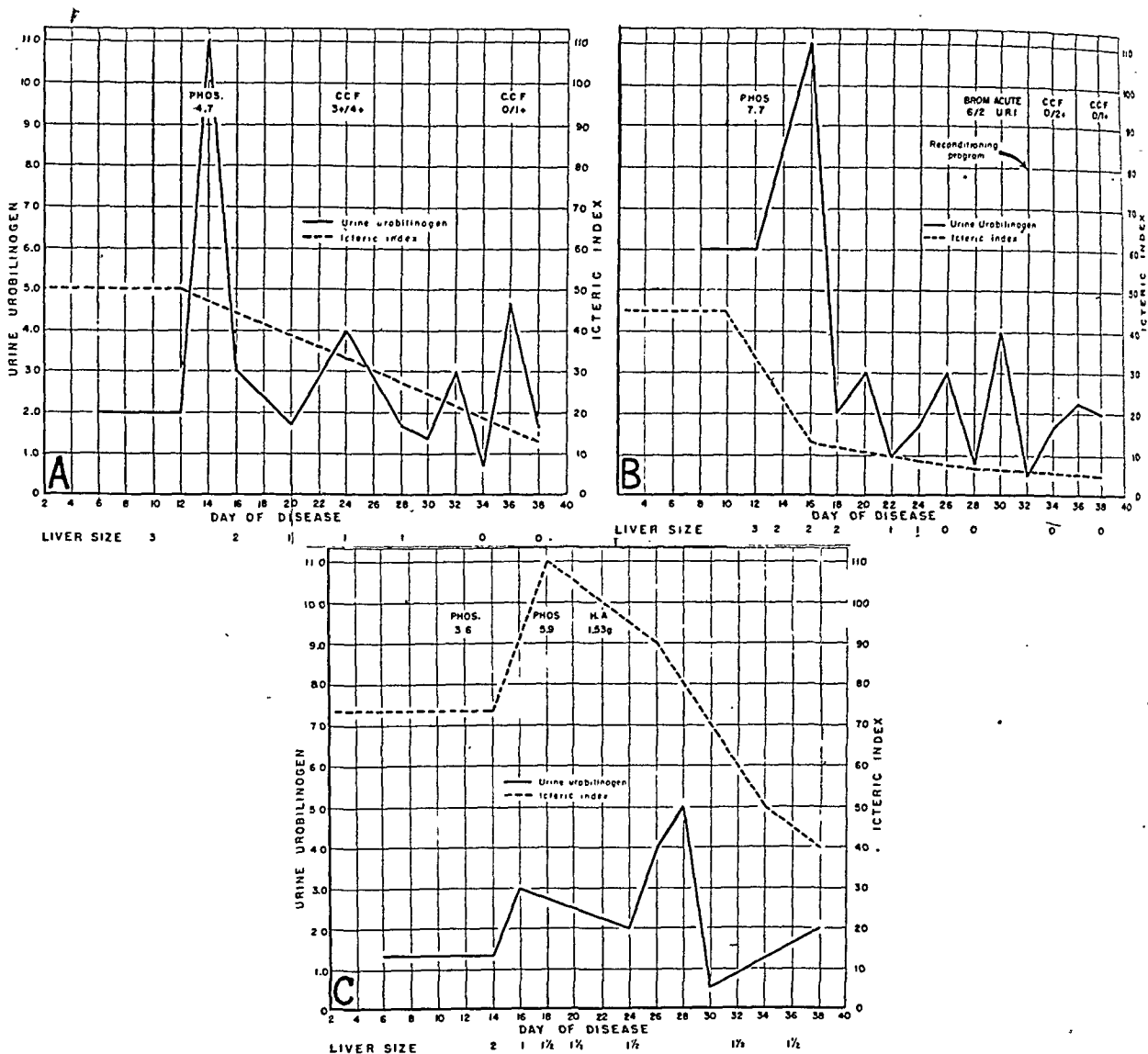


Fig. 1.—A, chart of a patient jaundiced for ten days before there was a decided rise in excretion of urobilinogen in the urine. After the icterus had begun to decrease, there were wide fluctuations in the amount of urobilinogen excreted, with some normal values occurring. Excretion was still abnormal after cephalin flocculation had become normal. Phos. indicates blood phosphatase; Brom., excretion of sulfobromophthalein (thirty minute and sixty minute readings), and C.C.F., cephalin-cholesterol flocculation (twenty-four to forty-eight hour reading). B, curve, similar to that in A, showing wide fluctuations in daily excretions. Abnormal amounts of urobilinogen in the urine were still being excreted after values in other tests of hepatic function had become normal. Note definite increase in values for urobilinogen as a result of an acute infection of the upper respiratory tract and early ambulation during the course of recovery. C, graph illustrates pronounced fluctuation of excretion of urobilinogen in the urine during active phases of acute hepatitis, even as the icteric index was approaching normal. Note that the patient had been jaundiced for two weeks before there was any striking increase in excretion of urobilinogen.

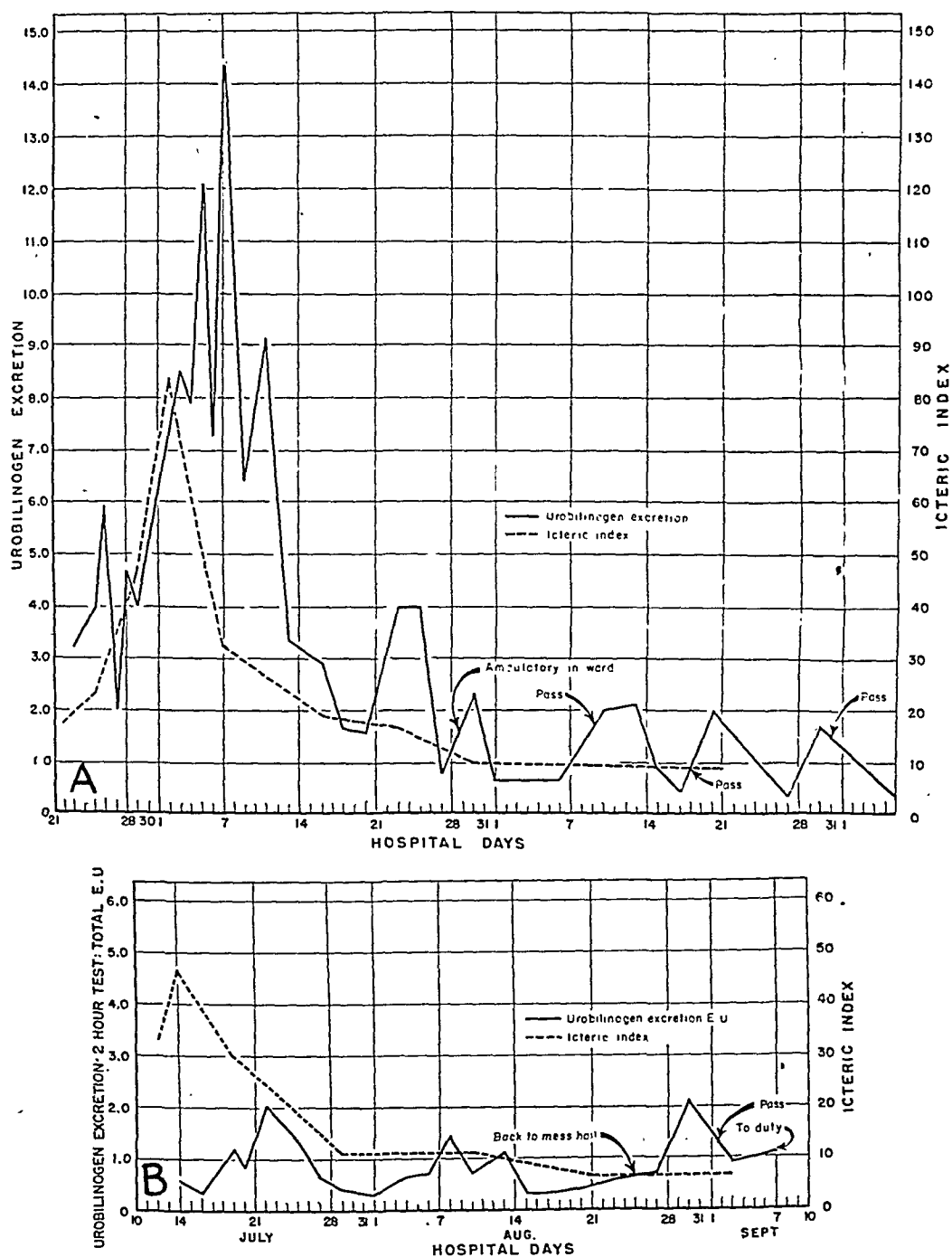


Fig. 2.—A, graph shows increase in excretion of urobilinogen in the urine corresponding to increase in values for icteric index as the peak of the illness is approached. After the icteric index begins to fall rapidly and reaches a normal level during the third week of the illness, there is a delay of fourteen days before the values for urobilinogen begin to approach normal. After the level of urobilinogen had become essentially normal, serial studies for urobilinogen in the urine revealed abnormal levels for thirty additional days. This was partially due to the effect of the patient's becoming ambulatory too early. The graph also illustrates the importance of serial studies of excretion of urobilinogen in the urine in an individual patient. The occasional normal levels found during the convalescent period may be misleading unless serial studies have been carried out. B, after levels of icteric index and excretion of urobilinogen had been normal for fourteen days, there was an immediate response in excretion of urobilinogen, but not in the icteric index, when the patient became ambulatory. One more week of rest was required before the level of urobilinogen became normal.

between the rise of the icteric index and the increase of excretion of urobilinogen (fig. 2). In most cases it was found that after the icteric index returned to normal and remained so the level of urobilinogen excretion would continue to fluctuate for two or three more weeks, depending on the patient's activity (fig. 2). After the values obtained in all other tests of hepatic function that were used, including the icteric index test, had become normal and the liver had not been palpable or tender for at least two weeks, the values for excretion of urobilinogen had a tendency to remain high for from several days to two weeks (fig. 3). In some cases in which clinical recovery seemed to be prompt and the icteric index dropped rapidly, there was a rather close correlation between the return of the excretion of urobilinogen in the urine

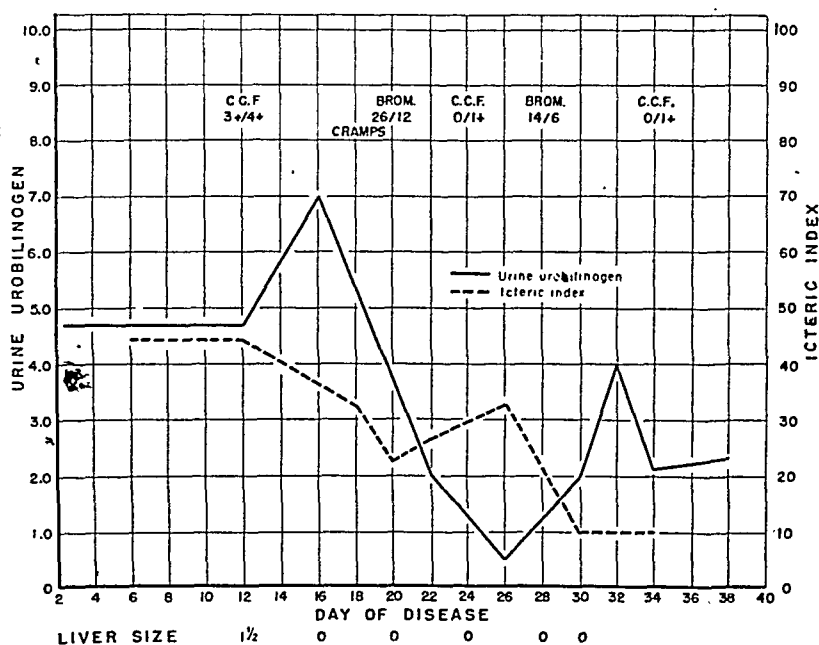


Fig. 3.—Graph illustrates the fact that values in all other tests of hepatic function had become normal and that the liver had been normal in size and non-tender for at least two weeks while increased levels of urobilinogen in the urine were still present. Note the decided increase in excretion of urobilinogen, which occurred on a day in which the patient had an acute gastrointestinal upset, which was probably related to the hepatitis.

and the icteric index to normal, providing the patient did not become ambulatory too early (fig. 4). If he became active too early, the value for urobilinogen excretion would remain elevated, finally becoming normal after a two or three week period if convalescence continued and no relapses interfered (fig. 5).

Summary.—The graphs reveal that it was desirable in each individual case to test the excretion of urobilinogen in the urine daily and to follow these levels until they had become normal. Only in this way could we decide, after the patient appeared to be clinically well, whether con-

valescence was actually completed or whether there was a tendency to relapse with increased activity. The number studied is too small to permit drawing conclusions, but it was our impression that patients were less liable to relapse when activity was forbidden until the excretion of urobilinogen in the urine had been within normal limits for about one week. Further study is needed in this direction.

Part 2.—For the purpose of adequate presentation of data, our series of 120 cases were divided into three classes on the basis of the intensity of the icterus at the height of the disease, as follows: (a) mild—icteric index less than 20 units (54 cases), (b) moderate—icteric index from 21 to 50 units (53 cases), (c) severe—icteric index more than 51 units

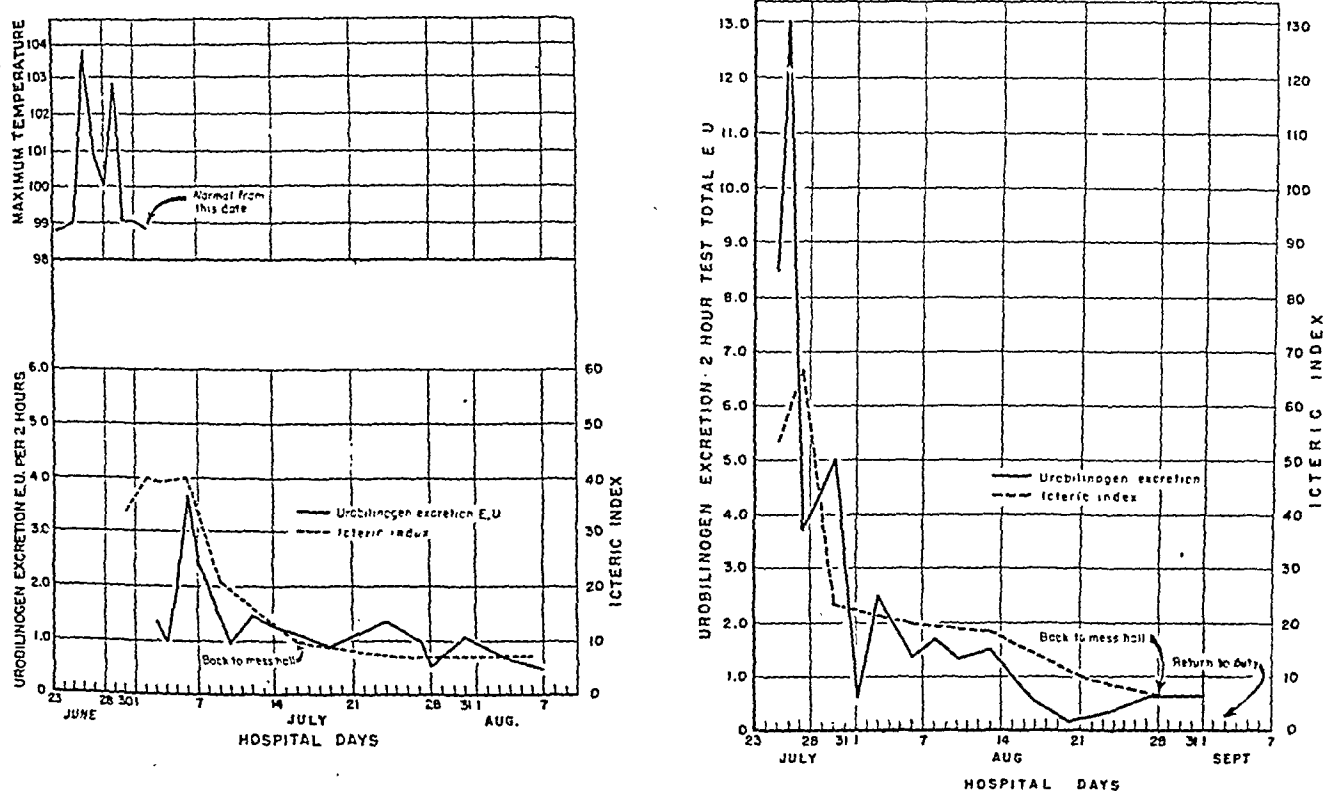


Fig. 4.—Graphs show the correlation between the fall of the icteric index and the rate of excretion of urobilinogen in the urine, with sustained normal levels in moderately ill patients with hepatitis who recovered rapidly without incident and who were kept in bed until recovery was complete.

(13 cases). In general, the classification agreed with the severity of the clinical symptoms.

In addition to the routine estimations of the icteric index, the following tests of hepatic function were performed on all patients for the purpose of comparison: (1) test for excretion of urobilinogen in the urine (two hour quantitative method of Watson), in which the normal value is 0.25 mg. (or 1 Ehrlich unit) or less for a two hour period, (2) a sulfobromophthalein retention test (using 5 mg. per kilogram of dye),

in which the normal value is 6 per cent or less retention after thirty minutes, (3) cephalin-cholesterol flocculation test (the twenty-four hour reading only is recorded in this report), in which the normal result is no flocculation and (4) test for activity of serum alkaline phosphatase, in which the normal value is less than 3.5 Bodansky units.

Plasma protein levels were determined many times, but they were not found to be significantly altered in all cases during the convalescent phases of the disease and for comparison purposes were not included in this report.

In table 1 are presented the results of tests performed while icterus was still evident. The values used in the calculation of each percentage were the most abnormal ones observed, and they may be assumed to represent the greatest deviation from normal encountered in indi-

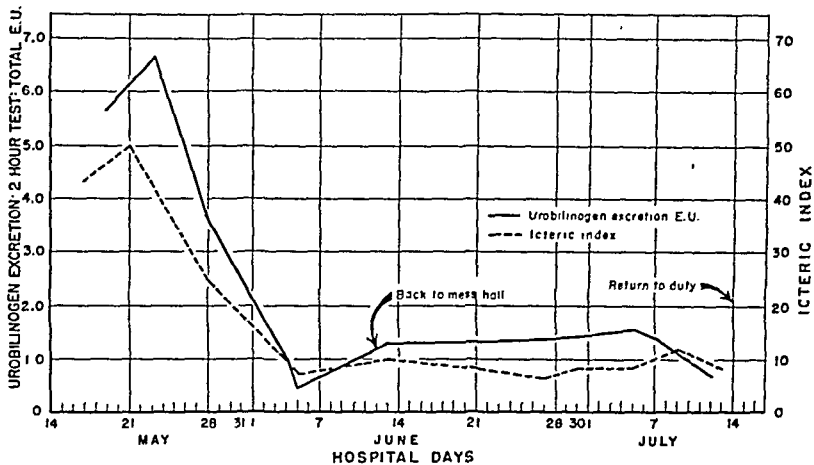


Fig. 5.—Increase in excretion of urobilinogen in the urine from normal to abnormal levels when the patient became ambulatory and remained so after the icteric index had become normal. Recovery was not complete until at least four weeks after the patient had become ambulatory and the icteric index had reached normal levels.

vidual cases. It is possible, of course, that had serial determinations of each test been performed the incidence of normal results might have been less. It has been common experience that many of the functional tests may not indicate abnormalities of function except as a result of extreme damage. Accordingly, the data are summarized to show in what percentage of each class normal values were obtained from a given test while icterus was still evident. Obviously, tests which give normal results at a time when the liver is certainly diseased have a limited value at best.

In table 2 the data are presented in a different manner. Many tests were performed after jaundice had disappeared, in an attempt to estimate the "residual hepatic damage" referred to previously. In this summary is given the percentage of cases in which each of the tests yielded

abnormal values during the first week or two after the icteric index became normal. It is a fair assumption from clinical experience that hepatic damage persists in patients with infectious hepatitis for some time after the jaundice disappears. A test which will indicate the existence of such damage is obviously of value, and its relative usefulness can be found by this method. After the icteric index became normal the tests outlined in table 2 continued to yield abnormal values.

TABLE 1.—*Results of Tests of Hepatic Function Performed While Icterus Was Present*

Normal values for excretion of urobilinogen in the urine were found in:

- (1) 20% of 35 cases of mild hepatitis
- (2) 17% of 41 cases of moderate hepatitis
- (3) 0% of 12 cases of severe hepatitis
- (4) 16% of all cases

Normal values for retention of sulfobromophthalein were found in:

- (1) 57% of 33 cases of mild hepatitis
- (2) 25% of 20 cases of moderate hepatitis
- (3) 20% of 5 cases of severe hepatitis
- (4) 43% of all cases

Normal values for cephalin-cholesterol flocculation were found in:

- (1) 60% of 17 cases of mild hepatitis
- (2) 40% of 22 cases of moderate hepatitis
- (3) 16% of 6 cases of severe hepatitis
- (4) 45% of all cases

Normal values for activity of serum alkaline phosphatase were found in:

- (1) 72% of 7 cases of mild hepatitis
 - (2) 35% of 17 cases of moderate hepatitis
 - (3) 25% of 8 cases of severe hepatitis
 - (4) 44% of all cases
-

TABLE 2.—*Hepatic Function in Patients After the Disappearance of Icterus*

-
- (1) Excretion of urobilinogen was abnormal in 77% of 18 cases
 - (2) Retention of sulfobromophthalein was abnormal in 43% of 46 cases
 - (3) Cephalin-cholesterol flocculation was abnormal in 38% of 34 cases
 - (4) Activity of serum alkaline phosphatase was abnormal in 30% of 10 cases
-

Summary.—On the basis of the data presented in tables 1 and 2 it is fair to conclude that of the tests studied the quantitative test for excretion of urobilinogen in the urine is the least likely to yield normal results during the period of jaundice and is the most likely to reveal abnormality immediately after the jaundice has disappeared.

SUMMARY AND CONCLUSIONS

A. One hundred and twenty cases of acute infectious hepatitis with jaundice were studied during the height of the disease and well into the convalescent period, a variety of the more sensitive tests of hepatic function being used.

B. Of the tests used, the quantitative method for determining the excretion of urobilinogen in the urine was found to be the most valuable. It was the test least likely to give normal results while jaundice was present and the one most likely to give abnormal results after jaundice had subsided.

C. Because of the simplicity of the test, serial studies of quantitative excretion of urobilinogen in the urine should be made at least every other day during the convalescent period of a patient with infectious hepatitis and interpreted in the light of this individual patient. Because of the wide fluctuations of excretion of urobilinogen in the urine during convalescence, a spot check may be misleading and normal values will be falsely interpreted.

PNEUMONIA ASSOCIATED WITH VARICELLA

Review of the Literature and Report of a Fatal Case with Autopsy

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IT HAS not been generally appreciated that varicella may occasionally assume the form of a rather severe disease, especially in adults, nor is pneumonia recognized as a common complication of this disease. A review of the medical literature on the subject shows a paucity of articles regarding it, and only 1 fatal case with autopsy observations has been described. It is therefore considered worth while to add another case to the literature, particularly as careful postmortem studies, including attempts at virus transfers, were undertaken.

Waldman¹ described a case of chickenpox in a Negro girl 8 years of age, in whom acute rheumatic endocarditis developed during the course of an ordinary uncomplicated attack, followed by lobar pneumonia of the lower lobe of the right lung, with a fatal termination on the tenth day of the disease. Autopsy was not permitted, but it was Waldman's opinion that the condition represented a concurrent infection rather than a complication.

Bullowa and Wishik,² studying 2,534 patients with chickenpox admitted to the Willard Parker Hospital in a four year period, found 8 deaths, 1 that of a patient over the age of 30. In the remaining cases the disease occurred in children less than 6½ years of age. In each of these cases slight to severe lobular pneumonia was described at autopsy. In this same series complications were noted in 5.2 per cent of all cases, pneumonia occurring in 0.8 per cent or representing one seventh of the complications.

Waring, Neubuerger and Geever³ described 2 cases of varicella and pneumonia, in 1 of which there was a fatal outcome; careful postmortem studies were made. A 40 year old man was admitted to the hospital

1. Waldman, S.: Complication, or Concurrence in a Case of Chickenpox Associated with Rheumatic Endocarditis and Fatal Pneumonia, *M. Rec.* **155**:9-10 (Jan. 7) 1942.

2. Bullowa, J. G. M., and Wishik, S. M.: Complications of Varicella: Their Concurrence Among 2,534 Patients, *Am. J. Dis. Child.* **49**:923-926 (April) 1935.

3. Waring, J. J.; Neubuerger, K. T., and Geever, E. F.: Severe Forms of Chickenpox in Adults with Autopsy Observations in a Case with Associated Pneumonia and Encephalitis, *Arch. Int. Med.* **69**:384-408 (March) 1942.

three days after the onset of his illness on Dec. 27, 1940. He gave a definite history of exposure to chickenpox through his son, who was convalescing from the disease. On admission to the hospital he was cyanotic and dyspneic, coughing frequently and expectorating a thick, tenacious and bloody sputum. He had a heavy but typical varicella eruption. The leukocyte count was 15,250, with 73 per cent neutrophils. Repeated smears and culture of the sputum failed to reveal pneumococci. Roentgenologic examination of the chest showed bronchopneumonia, with a widespread mottling through both lungs, most pronounced at the bases. In spite of intensive supportive treatment and the administration of sulfathiazole, progressive nitrogen retention developed, and he went into coma and died early on the seventh day of the disease. Postmortem examination disclosed (1) severe generalized chickenpox, (2) lobular pneumonia which was severe, confluent, mononuclear and proliferative, (3) acute, toxic, moderate, diffuse encephalitis with purpura of the white matter and (4) acute, toxic, moderate nephrosis.

The second patient was a 33 year old man with a definite history of exposure through his daughter. Severe chickenpox, acute bronchopneumonia, profuse bright bloody sputum, dyspnea, cyanosis, delirium, moderate nitrogen retention, pleurisy and osteomyelitis of the jaw developed, but he eventually recovered. He was first treated with sulfathiazole, and later given sulfanilamide when a pure culture of streptococcus was obtained from the sputum. He also received convalescent streptococcus serum, to which the authors give considerable credit for his eventual recovery.

Rausch, Grable and Musser⁴ present a report of a case of severe varicella in a 27 year old white male physician, complicated by pneumonia (said on roentgenologic examination to be a bronchopneumonic infiltration of both pulmonary fields) and by laryngeal spasm; the patient responded well to treatment with sulfathiazole.

An unusually severe outbreak of varicella among the natives of the French Cameroon district in 1936 was described by Millous.⁵ There were 1,919 cases, with 370 deaths, mostly involving adults. The disease appeared regardless of the smallpox vaccination which had been extensively employed in that area, with typical varicella lesions appearing in crops. In cases with a fatal outcome death was attributed either to nephritis with uremia or to severe laryngitis with prominent dysphagia and dyspnea. Unfortunately, no pathologic studies were reported for this outbreak.

4. Rausch, L. E.; Grable, T. J., and Musser, J. H.: Atypical Pneumonia Complicating Severe Varicella in Adult, *New Orleans M. & S. J.* **96**:271-275 (Dec.) 1943.

5. Millous: Une épidémie de varicelle maligne au Cameroun, *Bull. Acad. de méd., Paris* **115**:840-843 (June 16) 1936.

REPORT OF A CASE

The patient involved was a white housewife aged 32. On April 13, 1944, her 8½ year old son became ill with typical chickenpox. The disease ran its usual mild course without complications. On April 25 the patient complained to her husband that she did not feel as well as usual but continued her housework. On April 27 a typical chickenpox eruption commenced to break out, beginning over the head and thorax. Simultaneously, similar eruptions developed in the patient's other two children. All 3 were seen by a pediatrician, who made a diagnosis of chickenpox. The children had been successfully vaccinated against smallpox, and the patient herself thought that she had been vaccinated in childhood, although no scar was present.

On April 28 the patient commenced to complain of cough and abdominal pain, and on the advice of her pediatrician she called in an internist. She was first seen on April 29 at about 10 p. m. Physical examination at that time revealed a well nourished and well developed white woman, aged 32, whose arms, face and body were covered by a heavy maculopapular eruption in various stages and who appeared to be in moderate distress but not severely ill. She had a dry, harsh, nonproductive cough, which had been present for about eighteen hours, and also complained of vague colicky pain throughout the abdomen. There had been no nausea, vomiting or diarrhea and no hemoptysis. The temperature was 102 F. by mouth, the pulse rate 110 per minute and the respirations 20 per minute. The nose was moderately congested, and there were several enanthematous lesions over the palate and the buccal mucous membranes. One small pock was noted on the posterior pharynx. The face was covered with a heavy, typical varicella rash, which had spread over the thorax and axillary regions and which became lighter as it spread distally down the arms. A few lesions were noted on the legs, and one pock was noted on the palm of the left hand and one on the sole of the left foot. The lungs revealed somewhat roughened breath sounds at both apexes but were otherwise completely clear. The abdomen was soft and not tender. The heart was within normal limits on percussion and palpation. The rate was 110 per minute, the rhythm regular and the sounds of good quality, with no murmurs audible.

Calamine lotion had been used for the rash, and the patient was told that she might continue with the use of this. A cough mixture containing a small quantity of codeine was prescribed, and steam inhalations of tincture of benzoin were commenced.

On the morning of April 30 she complained of tightness in the chest, which became progressively severer and was accompanied with increasing dyspnea through the day. At noon she commenced to cough productively and brought up quantities of blood-tinged sputum. The temperature rose to 103.8 F. At this time she was admitted to the isolation ward of the Gallinger Municipal Hospital.

A review of systems was noncontributory. The past medical history revealed that the patient had had pneumonia as a young girl, from which she had recovered without difficulty. She had had one or two bouts of secondary anemia, which had responded to iron therapy, and her appendix had been removed. The family history revealed both parents to be living and well, and there was no history of familial disease. The husband, 36 years old, had had chickenpox and was perfectly well.

When admitted to the hospital, she was acutely ill, dyspneic and cyanotic. The rash was a little heavier than previously but was not confluent. The temperature was 102.6 F. by rectum, the pulse rate was 120 per minute, and the

respirations were short, shallow and rapid (50 per minute). There was considerable cyanosis of the lips and ears. Examination of the lungs revealed dulness on percussion over the left side of the chest, both anteriorly and posteriorly, extending over the entire lower two thirds, numerous harsh crepitant rales and scattered areas of tubular breathing in the left infraclavicular area. On the right side there was no impairment of resonance, but there were numerous inspiratory crepitant rales at the base. The observations in the remainder of the examination were essentially the same as those made in the home.

Immediately on the patient's admission to the hospital, sputum and blood were taken for typing and culture of the pneumococci, after which the patient was given 4 Gm. of sulfadiazine by mouth and then 1 Gm. every four hours. The temperature rose from 101 F. on admission to 104 F. on the following day and thereafter varied from 102.5 to 104 F., reaching 104.8 F. on the sixth day of the

TABLE 1.—Results of a Blood Count and a Urinalysis in the Patient Studied

Date	Blood Count									
	Red Blood Cell Count	Hemo- globin, %	White Blood Cell Count	Differential Count, %				Schilling Index, %		
				Neutro- phils	Lym- pho- cytes	Mono- cytes	Eosino- phils	Seg- mented Cells	Band Cells	Young Forms
4/30	4,510,000	88*	9,200	69	29	2	..	58	9	2
5/ 2	4,130,000	80	7,400	75	25	2	1	67	4	1
5/ 4	4,030,000	70	11,300	87	11	..	2	70	16	1

Urinalysis						
Date	Appear- ance	Reac- tion	Specific Gravity	Albu- min	Sugar	Acetone and Diabetic Acid
5/1	Dark amber	Acid	1.026	2+	Nega- tive	Nega- tive
5/3	Clear amber	Acid	1.015	2+	Nega- tive	Nega- tive
5/4	Dark amber	Acid	1.018	2+	Faint trace	Nega- tive

Microscopic	
A few hyaline and finely granular casts, 3 to 4 white blood cells per high power field; a few red blood cells and a few white blood cells; moderate number of hyaline and finely granular casts; few red blood cells and white blood cells per high power field	

* Newcomber.

illness. From this point there was a gradual but steady fall until death occurred. The pulse rate varied from 110 to 160 per minute and the respirations from 36 to 60 per minute.

Sputum.—On April 30 occasional pus and epithelial cells were found in the sputum, along with considerable blood. There were many gram-positive cocci, which appeared to be staphylococci and streptococci. There were no eosinophils, and no pneumococci were found on direct Neufeld typing. Culture revealed an occasional colony of type IV pneumococci (which in the opinion of the pathologist was due to a contamination from the mouth), *Streptococcus viridans*, *Staphylococcus aureus* and *Micrococcus catarrhalis*. No tubercle bacilli were cultured. On May 2 no pneumococci were found on direct Neufeld typing, and none were present on culture; there were no tubercle bacilli. *Str. viridans*, *Staph. aureus* and *M. catarrhalis* were again recovered.

Roentgen Examination.—Examination of the chest made on May 1, 1944 with portable x-ray equipment showed a homogeneous density in the lower half of the left lung and a diffuse bronchopneumonic type of infiltration throughout the remain-

ing portion of the pulmonary fields. The leaflets of the diaphragm were partially obscured by the infiltration. The heart and great vessels appeared to be within normal limits.

Course in Hospital.—Immediately on the patient's admission to the hospital, oxygen was administered by nasopharyngeal catheter. After eighteen hours an oxygen tent was used because the catheter proved irritating. The patient became progressively worse. On May 2 physical examination revealed complete involvement of the left side of the chest and considerable spread on the right, with rales and dulness over the lower two thirds both anteriorly and posteriorly. Hemoptysis continued, although less pronounced than on the date of admission.

After the finding of a prolonged bleeding time, coagulation time and prothrombin time on May 2, therapy with vitamin K was commenced. The patient was given 1.0 cc. intravenously. This was repeated in one hour, and then 20 drops were administered by mouth every four hours.

On May 3 the dosage of sulfadiazine was reduced to 0.5 Gm. four times daily, because of the high level (20 mg.) present in the blood.

By May 4 the patient was irrational at intervals. Respiration continued to be rapid and labored, and she was cyanotic even with continuous administration of oxygen. At 7 p. m. the dyspnea and cyanosis suddenly became much worse, the

TABLE 2.—*Results of Blood Tests*

Blood Culture	Blood Sulfadiazine Levels, %	Bleeding Time	Coagulation Time	Prothrombin Time	Nonprotein Nitrogen
4/30 : Negative	5/1 : 5 mg.	5/2 : 4 min. 30 sec.	4 min.	70 sec. (quick)	5/2 : 40 mg.
5/2 : Negative	5/3 : 20 mg. 5/5 : 8 mg.			55 sec.	

blood pressure fell to 70 systolic and 20 diastolic and there were other evidences of peripheral circulatory collapse. She received 250 cc. of blood plasma, 1,000 cc. of 5 per cent dextrose in isotonic solution of sodium chloride and 5 cat units of digifolin intravenously. She was then rapidly digitalized by the intramuscular administration of 1 cat unit every four hours for six doses. She responded well, and within three hours the blood pressure had returned to 110 systolic and 70 diastolic and she was partially oriented.

On May 5, at 6 a. m., the patient again appeared moribund. The respirations were 60 per minute, and the pulse rate was 120 per minute, being weak but regular. The blood pressure was 110 systolic and 60 diastolic, and she was unconscious. She rallied spontaneously from this episode, but her condition continued critical. She varied from a muttering delirium to violent attempts to pull the oxygen tent from her, screaming at intervals and apparently having vivid hallucinations. Reexamination of the chest late that afternoon revealed almost complete involvement of all pulmonary fields anteriorly. She was considered too ill to turn or be removed from the oxygen tent for posterior examination. Cyanosis and tachypnea persisted. At 10:56 that evening she suddenly died.

Treatment in addition to that already outlined included parenteral and oral administration of fluids to a level of 4,000 to 5,000 cc. in twenty-four hours. Pentobarbital sodium and codeine were used to allay pain and restlessness. Two hundred and fifty cubic centimeters of citrated whole blood was administered on May 3. On May 4 she received 150 cc. of whole blood from her convalescent 8 year old son, followed by 250 cc. of plasma. On May 5 she was given 500 cc. of

citrated blood from a patient who had recovered from varicella about three months previously.

Autopsy.—Postmortem examination was performed about nine hours after death. The body was that of a well developed and well nourished white woman. All the cutaneous surfaces were covered with a papular conical eruption. The centers of these lesions were slightly umbilicated, with crusting, and many showed hemorrhage. Some of the lesions were flatter and more vesicular, although the papular configuration was almost constant. They were not numerous on the scalp, and the skin between the lesions was not distended or otherwise abnormal. No lesions were noted on the conjunctiva or in the mouth.

On section, there was a normal layer of subcutaneous fat and the muscles were well developed. There was no free fluid in the abdominal cavity, and the abdominal organs appeared superficially normal. There was about 50 cc. of straw-colored fluid in each pleural sac, and a small amount of fibrin was present. The pericardial sac contained a normal amount of clear fluid.

The digestive tract showed a few small hemorrhages in the crests of the intestinal folds but was otherwise normal.

Spleen: The spleen was of average size, weighing 150 Gm. It showed several tiny white nodules 1 to 3 mm. in diameter in the capsule. Some of these were umbilicated and had small hemorrhages in their centers. Superficially, they resembled tubercles except for the umbilication. On section, the lymph follicles were prominent in the pulp and no lesions were noted on the cut surface.

Kidneys: The kidneys were both slightly larger than average, but their capsules stripped easily, leaving a smooth surface. On section, the parenchyma appeared normal save for slight cloudiness. A single small hemorrhage was noted in the cortex of the right kidney, just beneath the capsule, but its configuration was not unusual. Small hemorrhages were noted in the mucosa of the pelves, but they were otherwise normal.

The pancreas, bladder, uterus, adnexa and adrenal glands all appeared normal.

Liver: The liver showed a number of flat white nodules in the capsule on the upper surface of the right lobe near the anterior margin. Several of these were umbilicated and slightly raised above the surface, and hemorrhage was present in their centers. They varied from 2 to 5 cm. in diameter. They extended about 1 mm. into the parenchyma, but no other lesions were seen on section. The parenchyma was soft and pale. The gallbladder and bile ducts were normal.

The abdominal and mediastinal lymph nodes were slightly enlarged, soft and pale but showed no other unusual changes.

Lungs and Pleura: The pleural surfaces of both lungs showed scattered flat nodular lesions 3 to 8 mm. in diameter and were slightly raised above the surrounding surfaces. They were reddish white, and the centers were frequently depressed and showed hemorrhage. On section, there was extensive consolidation of all lobes of both lungs. The consolidation was widely scattered and consisted of numerous small nodules, usually about 5 mm. in diameter and frequently coalescent. Many of these nodules were hemorrhagic. They were more numerous in the lower lobes but were clearly evident in all the lobes. There was much congestion and edema in the lower lobes, but the upper lobes were more uniformly consolidated, with less congestion. The bronchi contained thick mucoid material, sometimes streaked with blood. The mucosa of the bronchi, trachea and larynx was slightly congested, but no distinctive lesions were found.

The heart and pericardium appeared normal.

Head: The calvarium and meninges appeared normal, and the external surface of the brain showed no abnormalities.

Microscopic Examination.—The lungs showed focal areas of pneumonic consolidation, especially about the small bronchi. The exudate was composed of fibrin and leukocytes, with polymorphonuclear leukocytes relatively inconspicuous. Small scattered areas of necrosis were also noted. In several areas there were prominent hyaline membranes lining the alveoli.

The liver showed necrosis of the cells in the central portions of the lobules, and there was deposition of fibrin and leukocytic infiltration. There were small nuclear inclusion bodies in some of the hepatic cells. No suppuration was evident.

The spleen showed focal areas of necrosis in, and just beneath, the capsule. These were somewhat larger than miliary tubercles. In these areas the tissues were disintegrated, and there were many fine granules, apparently derived from nuclear disintegration. The remainder of the pulp showed engorgement with red cells and leukocytes. The sinuses were large and distended.

Section of the skin revealed two crusted lesions showing ulceration of the surface epithelium. There was moderate leukocytic infiltration at the base of the ulcers but no distinct granulation tissue. Questionable inclusion bodies were noted in the nuclei of the epithelial cells.

The brain, pituitary, pancreas, adrenals, thyroid, kidneys and uterus showed no significant pathologic changes.

Tissues were obtained in glycerin and forwarded to the National Institute of Health for virus studies. Dr. Armstrong's report on their examination was as follows: "The material from your suspected fatal case of chickenpox was inoculated into monkeys, rabbits, rice rats and mice. All animals remained normal except 1 rabbit, which died in nine days of undetermined cause. Attempts at further transfers were unsuccessful."

COMMENT

The thought immediately arises as to whether this case might not have been an instance of atypical smallpox rather than of true varicella. The severe complications and fatal outcome, plus the absence of a scar from smallpox vaccination, suggest this possibility.

Militating against this diagnosis are: first, the presence of typical chickenpox in 1 child in the family plus the simultaneous occurrence of the disease in the other 2 children (who had been successfully vaccinated against smallpox) and the mother within the expected incubation period; second, the history of vaccination in the mother, and, third, the typical varicella character and distribution of the cutaneous lesions (vesicular eruption with umbilication appearing in crops and concentrated most heavily on the head and trunk). The weight of this evidence seems definitely in favor of a diagnosis of chickenpox.

The similarity of the 2 cases reported by Waring, Neubuerger and Geever to this one is striking, with the rapid early pulmonary involvement and the hemoptysis being outstanding in all 3.

It is unfortunate that the virus transfers attempted at the National Institute of Health were not successful. The reasons for this may have been: (1) the length of time between the outbreak of the disease and its fatal termination on the eighth day and (2) the length of time elapsing

between death and the performance of the postmortem examination (twelve hours).

A striking feature of the postmortem examination was the presence of what were apparently varicella pocks on the pleura, within the pulmonary tissue and on the peripheral portions of the liver and spleen. Microscopic examination confirmed the apparently pocklike nature of these lesions.

SUMMARY

The literature relating to fatal cases of varicella (chickenpox) is reviewed, and an additional fatal case, with postmortem studies and attempts at virus transfer, involving a previously healthy adult is presented.

It is again emphasized that a disease, usually considered to be a relatively harmless and innocuous one, may on occasion become severe and fulminating.

The study of this case was aided by the National Institute of Health and Dr. Armstrong, responsible for the attempted virus transfer; Dr. Arnold McNitt and Dr. Roy Adams, of Washington, D. C., who saw the patient in consultation, and Dr. Thomas Peery and Dr. Roger Choisser, of the Department of Pathology of the George Washington University Medical School, who made the careful postmortem examination.

CONCENTRATION TEST OF RENAL FUNCTION USING POSTERIOR PITUITARY INJECTION

An Evaluation

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THE ability of the normal kidney to produce a concentrated urine under conditions of diminished intake of fluid is usually the first function to fail under the influence of renal disease. Procedures designed to test this function of the kidney are the most useful and the least complicated to perform. The technics described by Fishberg¹ and by Addis and Shevky² are time-tested standards for routine use. They require the production of oliguria by depriving a tested subject of fluids over an interval of from sixteen to twenty-four hours and the measurement of the specific gravity of samples of urine voided at the end of this period of restriction. The maximum specific gravity necessary for evaluation of renal concentrating capacity may not be attained under the following conditions: (a) if the patient fails to cooperate, often because of excessive thirst, and drinks fluid during the period of deprivation; (b) if the period of abstinence from fluids is not sufficiently long to test renal concentrating capacity adequately in patients who have been drinking excessive amounts of fluid prior to the test, or (c) if edema fluid is being cleared.

Utilization of the antidiuretic action of posterior pituitary extract to eliminate the period of imposed interdiction of fluid and thus to circumvent sources of error and to simplify the performance of renal concentration tests was first thoroughly investigated by Sodeman and Engelhardt,³ though references to similar procedures have appeared

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Part of this work was done while Dr. Schneeberg was at the Mount Sinai Hospital in Philadelphia, and part was done while he was in army service.

1. Fishberg, A. M.: *Hypertension and Nephritis*, ed. 4, Philadelphia, Lea & Febiger, 1939, p. 74.

2. Addis, T., and Shevky, M. C.: A Test of the Capacity of the Kidney to Produce Urine of High Specific Gravity, *Arch. Int. Med.* **30**:559-562 (Nov.) 1922.

3. Sodeman, W. A., and Engelhardt, H. T.: (a) Renal Concentration Test Employing Use of Pituitary Extracts: Response of Normal Subjects, *Proc. Soc. Exper. Biol. & Med.* **46**:688-691 (April) 1941; (b) A Renal Concentration Test Employing Posterior Pituitary Extract, *Am. J. M. Sc.* **203**:812-818 (June) 1942.

in the literature since 1921.⁴ Their test now appears in a standard text of laboratory procedures,⁵ and its use has been advocated in two recent reviews.⁶ Wall,⁷ Taylor, Peirce and Page⁸ and Schneeberg, Likoff and Rubin⁹ have published their experiences with this test, with varying conclusions as to its acceptability for general use. Concern for possible untoward effects of posterior pituitary has been expressed. It is my intent to reevaluate this procedure and to show the effect of administration of posterior pituitary (posterior pituitary injection U.S.P. was used) on the electrocardiogram, the blood pressure and the pulse rate of patients subjected to the test.

METHODS

A. Renal Concentration Tests.—Renal concentration tests were as follows: (1) the Fishberg concentration test, which was performed as outlined by its author¹; (2) the concentration test with posterior pituitary injection, in which, without restriction of fluid or food, the patient emptied his bladder, 10 units of posterior pituitary was injected subcutaneously and three specimens of urine were obtained hourly thereafter; (3) the Volhard dilution test, in which the subject emptied his bladder and drank 1,500 cc. of water within thirty minutes and then four hourly specimens of urine were collected; (4) a test in which procedure 3 was repeated with the addition of 10 units of posterior pituitary injected subcutaneously after the ingestion of the fluid; (5) the Addis concentration test; in this test the subject abstained from fluid for twenty-four hours (from after breakfast of one day until arising the next morning) and then the urine of the last twelve hours of this period was collected and the specific gravity measured.

The specific gravity of the urine was measured with a clinical urinometer calibrated with distilled water at a standard temperature. Appropriate corrections for variations in temperature¹⁰ and protein content¹¹ were made.

Procedures 1 and 2 were carried out on 136 subjects comprising 101 normal persons and 35 with varying evidences of renal disease. For 25 of the normal subjects procedures 1, 2, 3 and 4 were carried out, and 15 additional persons

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11. Lashmet, F. H., and Newburgh, L. H.: Improved Concentration Test of Renal Function: Simple Method for Measuring Proteinuria, *J. A. M. A.* **100**:1328 (April 29) 1933.

were subjected to procedures 1, 2 and 5. For the purposes of this study a specific gravity of 1.020 was arbitrarily chosen as a basis for the division of the patients into two groups. Those with a concentration of 1.020 or better were considered "normal" and those with a concentration of 1.019 or less were considered "abnormal." In the Addis test the patient was considered normal if a specific gravity of 1.026 or higher was attained.

B. Cardiovascular Investigation of the Effects of Posterior Pituitary Extract.—These observations were made in a small, well ventilated, warm room free of external sources of stimulation. All procedures were carried out by me. The subject lay supine on a bed for forty-five to sixty minutes, after which the pulse rate and blood pressure were taken every five minutes until a stabilized level was maintained. Subjects with labile pressures or variable pulse rates were not used. Electrodes were then applied, and an electrocardiogram in the limb leads and CF IV was taken. The blood pressure and pulse rate were again checked to

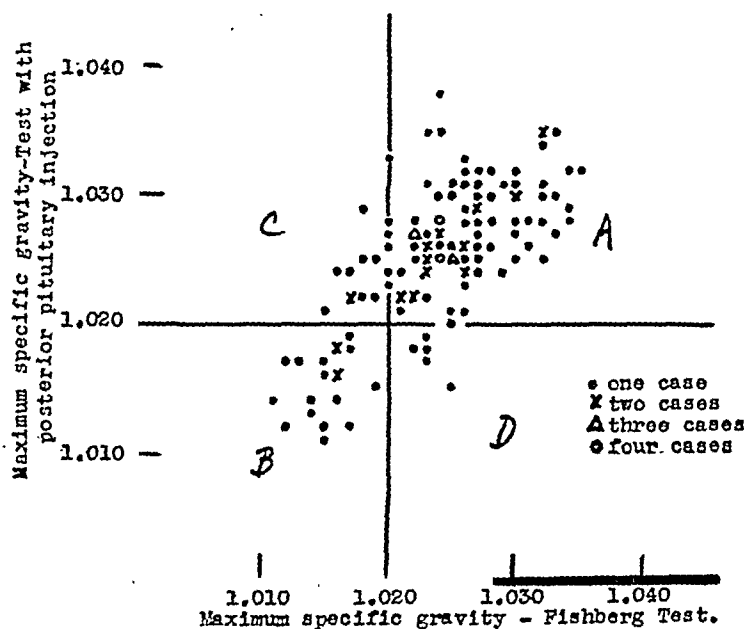


Chart 1.—A comparison of the maximum concentrations of urine obtained by the Fishberg test and by the test with posterior pituitary injection.

insure that the basal level was maintained, and 10 units of posterior pituitary was injected subcutaneously. The blood pressure and pulse rate were taken thereafter every five minutes for a half hour and at forty-five, sixty and ninety minutes. Electrocardiograms in the four leads were taken ten, twenty, thirty, forty-five, sixty and ninety minutes after the injection. The sphygmomanometer cuff and the electrodes were left in place throughout the experiment.

In 5 patients the blood pressure and pulse rate were similarly measured before and after the subcutaneous injection of 0.5 cc. of sterile isotonic solution of sodium chloride.

RESULTS

A. Renal Concentration Tests.—In chart 1 the maximum concentrations of urine obtained by the use of posterior pituitary injection and by the Fishberg test are given for 136 cases. One hundred and two of these patients, comprising group A of the graph, had a concen-

tration of 1.020 or better by both tests, exhibiting, according to the criterion established, normal concentrating ability. Nineteen patients, comprising group B on the graph, had a concentration of 1.019 or less by both tests, exhibiting an inability to concentrate urine normally. In group C, comprising 10 cases, the tests failed to achieve comparable results. Normal concentrations of urine were obtained by the use of posterior pituitary injection when, in the same patient, abnormally dilute urine was obtained in the Fishberg test. In group D, comprising 5 cases, the tests again failed to yield comparable results. In these cases the Fishberg test produced a normally concentrated urine and the test with posterior pituitary an abnormally dilute urine. Thus the posterior pituitary test failed to estimate renal concentrating capacity properly in 3.7 per cent of the 136 cases, and the Fishberg test similarly failed in 7.4 per cent. These stated percentages of failure, how-

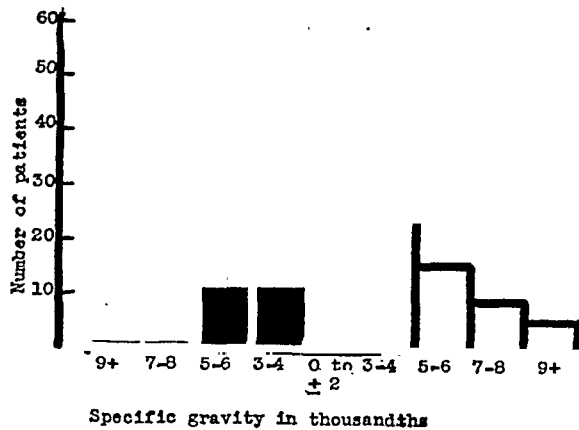


Chart 2.—Distribution graph of the differences between the test with posterior pituitary injection and the Fishberg test in 136 patients. The former test gave the higher value to the right of the solid block, and the latter gave the higher value to the left.

ever, are not significant, because a change of the arbitrarily established criterion of normal from 1.020 to 1.022 or 0.023 will greatly alter the results. The individually plotted specific gravities in chart 1 are well grouped about a straight line curve, and the distribution graph shows a normal scatter about the mean. The only conclusion that is justified, therefore, is that in the 136 cases examined the two tests yielded similar results.

In chart 2 the distribution of the differences between the two tests is graphed. In 17 patients identical maximum specific gravities were obtained by the test with posterior pituitary injection and the Fishberg test. The former test yielded the higher specific gravity in 79 cases, and the latter yielded the higher result in 40 cases. The difference in specific gravity in the two tests was 0.004 or less for 69 per cent of the 136 patients and 0.006 or less for 89 per cent.

Chart 3 graphically illustrates a comparison of three tests for concentration of urine performed on the same patient (procedures 1, 2 and 5). In 11 patients the results in all three tests agreed, 6 showing normal concentration of urine and 5 abnormal concentration. In 4 cases in which the Addis test and the posterior pituitary test showed normal results, the Fishberg test gave abnormal values. Thus the posterior pituitary and the Addis test agreed in their estimate of renal function in all 15 cases.

In the 25 subjects in whom procedures 3 and 4 were performed, the average specific gravity was 1.006 as obtained by procedure 3 and 1.024 as obtained by procedure 4. This indicated the potency of the preparation of posterior pituitary injection used.

B. *Cardiovascular Investigation.*—No significant changes were noted in the electrocardiograms taken after the injection of the posterior

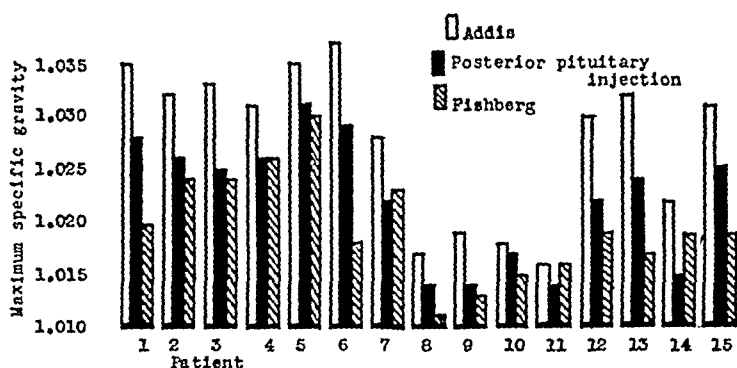


Chart 3.—A comparison of three concentration tests of renal function performed on each of 15 patients.

pituitary extract. The seven tracings obtained in each patient either were identical or showed insignificant variations.

Chart 4 graphically portrays the changes in blood pressure noted after the use of posterior pituitary injection compared with the blood pressure in controls who received injections of isotonic solution of sodium chloride. The mean curves for the two groups are similar except for the systolic and diastolic rise, which occurred five minutes after the injection of posterior pituitary extract and subsided to the basal level within fifteen minutes for the systolic pressure and twenty minutes for the diastolic pressure. Since this change was not observed in the control patients, it appears to be a specific effect of the pituitary extract. The gradual fall in average pressures below the basal level probably represents the effect of the long-continued supine position that the experiment entailed, since it was noted in both groups. In individual cases a much greater rise or fall from the basal level was encountered in the subjects receiving posterior pituitary injection than in the controls receiving isotonic solution of sodium chloride. This

is evidenced by the widely scattered systolic pressure readings in chart 4.

Posterior pituitary injection caused a slight rise in the mean pulse rate ($4\frac{1}{2}$ per minute, with a range of plus 18 to minus 8) in the five and ten minute periods after the injection, which did not occur in the controls. This acceleration of the pulse rate was, therefore, probably due to the action of the pituitary extract rather than a nonspecific reaction to a hypodermic injection.

COMMENT

The data presented indicate that the use of posterior pituitary injection in renal concentration tests in 136 patients yielded results that

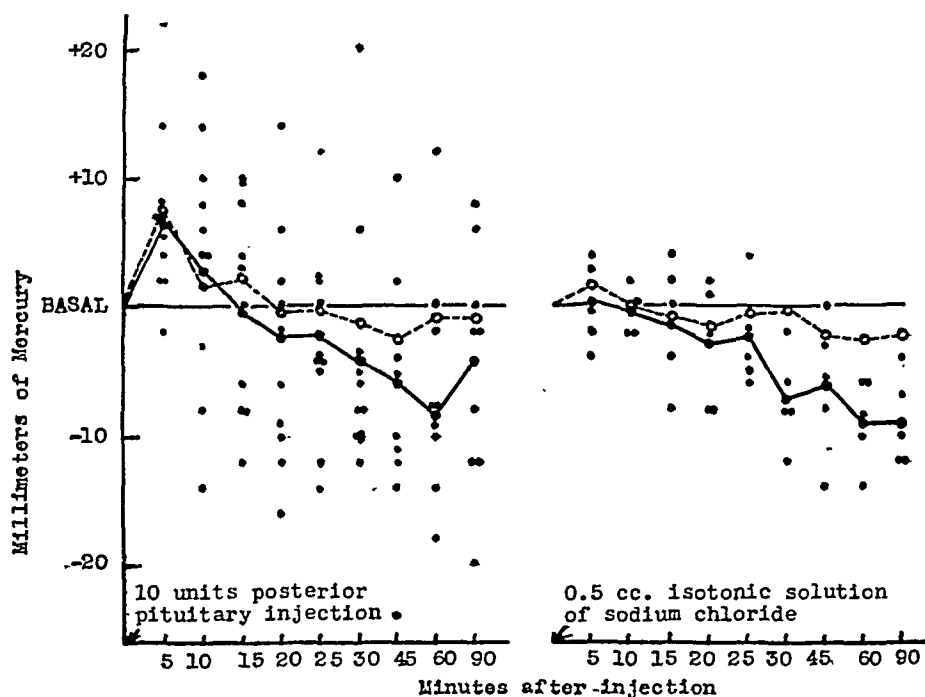


Chart 4.—Mean changes in blood pressure after the subcutaneous injection of posterior pituitary extract in 10 patients and normal isotonic solution of sodium chloride in 5 controls. Unconnected points are individual systolic pressure readings. The broken line indicates the mean diastolic pressure and the unbroken line the mean systolic pressure.

were similar to those obtained in the standard Fishberg test. The test with posterior pituitary injection may, therefore, be used routinely whenever a concentration test of renal function is indicated.

While Sodeman and Engelhardt³ and Wall⁷ found the posterior pituitary test reliable, Taylor, Peirce and Page⁸ concluded that it was not entirely acceptable in clinical practice. They compared it with the procedure, outlined by Addis and Shevky,² in which fluids are interdicted for twenty-four hours. Much greater average concentra-

tions of urine were promoted by the Addis test than by the posterior pituitary test or by the use of pitressin tannate in oil, short periods of dehydration and combinations of these. Said the authors: "None of these procedures attained the mean concentration of 1.030 recorded after 24 hours dehydration in normal subjects." The range of variation in them was from 1.016 to 1.033, compared with 1.026 to 1.032 in the Addis test. Similar variability was observed in abnormal subjects receiving pituitary extracts. They also discussed untoward effects resulting from the injection of posterior pituitary extract.

In the present study the Addis test was compared with the Fishberg test and the posterior pituitary test in the same patients, and it was found that a twenty-four hour fast from fluids gave no more useful information than did the posterior pituitary test in the subjects investigated. In each instance both technics yielded results which agreed in the estimation of tubular concentrating ability according to the standards established. The results of this comparison in chart 3 show that the Addis test produced the highest specific gravity in 14 of the 15 patients and that in the remaining patient (case 11) both the Addis and the Fishberg test produced a specific gravity of 1.016 and the posterior pituitary test a value of 1.014. If, however, one accepts 1.026 as the normal value for the Addis test,² a similar failure to achieve normal concentrations of urine was noted in the same patients exhibiting impaired concentrating ability by the other tests. The Fishberg test and the posterior pituitary test do not give ceiling values, but they do give results that are consistent and clinically applicable. The Addis test requires a twenty-four hour period of abstinence from fluid and can be properly performed only in a hospital ward adequately staffed to control the conditions of the test.

The test with posterior pituitary injection is ideally designed for office practice because of its simplicity, the speed with which results are obtained and the elimination of the hardship imposed on the patient by abstinence from fluid and by the necessity of carrying urine to the office. Unlike the tests requiring the interdiction of fluids, it will not fail to produce a concentrated urine even if the patient is edematous.⁷ Its effect is dissipated within six hours, and edematous reservoirs can be cleared as before. In febrile or surgical patients in whom deprivation of fluid is not desired, the test with posterior pituitary injection may be used when the Addis or Fishberg test would be impractical.

Significant cardiovascular changes were not produced by the injection of the recommended dose of posterior pituitary used in the test for renal function aside from a transient rise in blood pressure and

increase in pulse rate in the period immediately following the injection. Similar results have been reported by others.¹²

Because of the well known coronary-vasoconstrictive effect of posterior pituitary, coronary arterial disease and angina pectoris are considered contraindications to its use. Graybiel and Glendy^{12c} gave 20 international units of pitressin intravenously to 2 patients with "easily provoked anginal pain." Though this dose was sufficient to provoke abdominal cramps, anginal pain did not occur. Wall's patient with angina pectoris⁷ experienced slight substernal distress and tingling down the left arm following the injection of posterior pituitary extract, which promptly disappeared after administration of glyceryl trinitrate. My colleagues and I⁹ observed no untoward effects when using the test in patients with coronary arterial disease, but because of the theoretic objections mentioned previously, the tests using deprivation of water are preferred for such subjects. The subcutaneous injection of posterior pituitary extract causes a mild burning sensation at the site of injection, lasting two to three minutes. Most persons experience no subsequent discomfort, though the occasional patient, on being questioned, will describe slight shortness of breath, substernal warmth, a "cool feeling across the chest," a slight "cool sensation all over" or fleeting nausea. Slight pallor of the skin can be observed shortly after the injection in about one quarter of the cases.

The paucity of reports of hypersensitivity to posterior pituitary is striking when one realizes how commonly this extract is used. In more than 350 persons subjected to the posterior pituitary test by various workers, there has been no instance of hypersensitivity or an anaphylactic reaction reported. McMann¹³ could find only twelve references to reactions indicating sensitivity up to 1939 and added two of his own, Werner¹⁴ stated that he has had experience with approximately two hundred thousand injections of posterior pituitary extract without harmful results. Grand mal seizures may be precipitated by effective anti-

12. (a) Moffat, W. M.: The Effect of Pituitrin Injections on Blood Pressure in Man, *Am. J. M. Sc.* **186**:854-860 (Dec.) 1933. (b) Grollman, A., and Geiling, E. M. K.: Cardiovascular and Metabolic Reactions of Man to Intramuscular Injection of Posterior Pituitary Liquid (Pituitrin), Pitressin and Pitocin, *J. Pharmacol. & Exper. Therap.* **46**:447-460 (Dec.) 1932. (c) Graybiel, A., and Glendy, R. E.: Circulatory Effects Following the Intravenous Administration of Pitressin in Normal Persons and in Patients with Hypertension and Angina Pectoris. *Am. Heart J.* **21**:481-489 (April) 1941.

13. McMann, W.: Hypersensitivity to Solution of Posterior Pituitary, *J. A. M. A.* **113**:1488 (Oct. 14) 1939.

14. Werner, A. A.: *Endocrinology: Clinical Application and Treatment*, ed. 2. Philadelphia, Lea & Febiger, 1942, p. 75.

diuresis with posterior pituitary injection if fluids are forced.¹⁵ One death by such a provocative procedure has been reported.¹⁶ The use of posterior pituitary injection in epileptic patients had best be avoided, though it seems unlikely that the injection of a single dose of 10 units without the administration of extra fluid could precipitate a seizure.

The contraindications to the use of posterior pituitary injection in tests of renal function are as follows:

A. Absolute contraindications.

1. Hypersensitivity to posterior pituitary extract.
2. Pregnancy.
3. Severe coronary arterial disease (myocardial infarction, acute coronary insufficiency or angina pectoris decubitus).

B. Probable contraindications.

1. Angina pectoris.
2. Epilepsy.

In clinical practice the test may be performed as follows:

1. It may be carried out at any time without preparation.
2. The patient voids, emptying his bladder completely. If the specific gravity of this specimen is 1.022 or higher, the test need not be done. If the specific gravity is 1.021 or less, the test is carried out.
3. A 10 unit dose of posterior pituitary injection U.S.P. is introduced subcutaneously.
4. Urine is collected in one and two hours. When the volume of the two specimens is too small to permit measurement of specific gravity with the clinical urinometer, a specimen is collected after three hours.
5. Normal subjects will have a specific gravity of 1.022 or better in one specimen. The criterion of 1.020 used in this study was arbitrarily selected for the purposes of comparing the posterior pituitary test with the Fishberg test.

SUMMARY

1. A comparison of the concentration test of renal tubular function in which posterior pituitary injection is used with the standard Fishberg test in 136 patients showed that this new procedure yields sufficiently similar results to be used routinely as a substitute test.

15. McQuarrie L., and Peeler, D. B.: The Effects of Sustained Pituitary Antidiuresis and Forced Water Drinking in Epileptic Children: A Diagnostic and Etiologic Study, *J. Clin. Investigation* 10:915-940 (Oct.) 1931.

16. Muller-Suur, H.: Death Due to Tonephin (Posterior Pituitary Preparation) Injection for Diagnostic Provocation of Epileptic Attack by Water Retention, *Psychiat.-neurol. Wchnschr.* 44:137-139 (May 2) 1942.

2. The Addis test, requiring a twenty-four hour fast from fluids, gave no more useful information in the same patient than did the test with posterior pituitary injection, despite its ability to produce ceiling values in most instances.

3. Posterior pituitary injection, in the dose used in this test, produced no significant electrocardiographic changes and only a transient rise in blood pressure and acceleration of pulse rate.

4. Hypersensitivity to posterior pituitary is extremely rare and has not been encountered in the performance of this test.

5. Contraindications to the use of posterior pituitary are outlined.

6. The test is simple to perform and avoids sources of error inherent in tests requiring periods of abstinence from fluid.

1930 Chestnut Street.

STUDIES ON THE CAUSATION OF AN UNUSUAL PULMONARY DISEASE AT CAMP GRUBER, OKLA.

COMMISSION ON ACUTE RESPIRATORY DISEASES

in Collaboration with

FIRST LIEUTENANT WALTER A. MICKLE Jr.

SANITARY CORPS, ARMY OF THE UNITED STATES

Specimens of sputum from 17 patients with pneumonia at Camp Gruber, Okla., have been examined for the presence of an infectious agent which might have caused the illnesses. Most of the sputums were obtained three to four weeks after the onset of the disease, but many of the patients were still febrile at the time of collection. In addition, sputums were collected from 8 patients not involved in this outbreak of pneumonia for the purpose of comparison.

Several samples of dust from a storm cellar, incriminated epidemiologically as a probable source of the infection, and of dirt from a nearby machine gun emplacement were also collected for study.

Cultures, inoculation of animals and serologic tests were carried out. Particular emphasis was placed on mycologic examinations, because of the clinical characteristics of the disease.

EXPERIMENTAL DATA

Cultures for Bacteria.—Cultures for bacteria in the sputums were made on blood agar plates. These were examined after twenty-four and forty-eight hours of incubation. Representative colonies of bacteria were isolated and identified.

No one species of bacteria was predominant in any of the cultures. Small numbers of hemolytic *Staphylococcus aureus* were recovered from 10 of the 17

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Members and associates of the Commission on Acute Respiratory Diseases are: Major John H. Dingle, Director; Major Theodore J. Abernethy; Major George F. Badger; Major Norman L. Cressy; Major Alexander D. Langmuir; Capt. Hugh Tatlock, and Capt. Elias Strauss, Medical Corps, Army of the United States; and Dr. J. W. Beard, Dr. A. E. Feller, Dr. Irving Gordon and Dr. Charles H. Rammelkamp.

patients with pneumonia and from 1 control patient. Group A beta hemolytic streptococci were recovered in small numbers from 2 patients. The samples of dust and dirt were not cultured for bacteria.

Cultures for Fungi.—Cultures for fungi were made on Sabouraud's dextrose agar and dextrose-tartaric acid agar. These cultures were examined at intervals for four weeks before they were discarded. Fungi were isolated as soon as they appeared and were identified by standard mycologic methods.

Aspergillus, *Penicillium*, *Mucor*, *Rhizopus*, *Alternaria*, *Fusarium*, *Saccharomyces* and aerobic *Actinomyces* were isolated from the sputums. These were not identified further. *Aspergilli* were isolated from 5 patients with pneumonia and *Penicillium* from 3 patients. *Mucor* and *Rhizopus* were isolated from 2 patients each, and *Saccharomyces* and aerobic *Actinomyces* occurred only once. *Candida pseudotropicalis* was isolated from 1 patient. *C. albicans* was isolated from 10 of the 17 patients, but in only one instance were there more than four colonies on the plate.

Aspergillus was isolated twice and *Penicillium* and *Mucor* once from the sputums of the 8 controls.

Samples of dust from the cellar and of dirt from the gun emplacement yielded a variety of molds: *Mucor*, *Aspergilli*, *Penicillium*, aerobic *Actinomyces*, *Alternaria* and *Rhizopus*. No *C. albicans* was found.

Inoculation of Animals.—Specimens of sputums were inoculated intranasally and intraperitoneally into mice, cotton rats, hamsters, guinea pigs and monkeys. Records of the daily temperature were kept on the hamsters, guinea pigs and monkeys. Roentgenograms of the chest were taken on the monkeys at two to three day intervals before and for six weeks following inoculation.

No evidence of significant illness occurred in any of the animals. One animal of each species in the groups inoculated intranasally and intraperitoneally was killed eleven days after inoculation. None of these animals showed gross or microscopic evidence of infection, and cultures of the internal organs for bacteria and fungi were sterile.

Two strains of *C. albicans* isolated from sputums of patients with pneumonia were tested for virulence in guinea pigs and rabbits. One cubic centimeter of a 10 per cent suspension was necessary to kill the animals, indicating a relative lack of virulence.

Serologic Studies.—Tests with *C. albicans* on serums from each of 15 patients in the acute and convalescent stages of pneumonia and from 8 control patients showed no agglutination or complement fixation above a dilution of 0.125 in any case. There were no rises in titer in the serums from convalescent patients.

Agglutinins for the rickettsia of Q fever and cold hemagglutinins for group O human erythrocytes were not found in the serums from convalescent patients.

CONCLUSION

Studies on specimens from patients with pneumonia occurring at Camp Gruber, Okla., have failed to identify a causative agent. Attempts to reproduce the disease in animals were unsuccessful. Although *C. albicans* was isolated in 10 of 17 patients ill with pneumonia, the role of this organism is questionable because of the lack of supportive evidence.

NOTE.—This material should have been published as supplement to the article by Colonel James C. Cain, Major Edward J. Devins and Lieutenant Colonel John E. Downing, "An Unusual Pulmonary Disease," in June 1947 (*Arch. Int. Med.* 79:626, 1947).

RECENT MYOCARDIAL INFARCTION

An Analysis of Five Hundred and Seventy-Two Cases

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CONSIDERABLE modification has occurred in the point of view concerning recent myocardial infarction since its first adequate clinical description by Herrick.¹ There is therefore need for further studies of this condition. The present report deals with the cases of recent myocardial infarction in which electrocardiographic studies were made at the Michael Reese Hospital in the period from Jan. 1, 1940 to Dec. 31, 1945. Only the cases were included in which, on the basis of the history, the electrocardiograms and, when available, the observations at autopsy, the condition could unequivocally be diagnosed as a recent myocardial infarct. A total of 572 cases was selected. The patients for the most part were Jews; a few were Negroes.

Of the total of 572 patients, 504 were admitted to the hospital for a six to eight week (rarely a ten week) stay as ward and private patients; on these, complete histories, serial electrocardiograms and the usual laboratory data were available. For 48 of the patients, who were kept at home by their private physicians during the acute stage of the disease, the data available to us consist of electrocardiograms made during convalescence. In addition, their age and sex and the date of the attack are known. The remaining 20 patients, from the outpatient clinic, were also kept at home during the acute stage; information on them was obtained from their physicians, the social service worker, their clinic records and the electrocardiograms taken during the initial and convalescent stages of illness.

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The attending physicians of the patients included in this study permitted us to use the records of their cases and in many instances supplied us with additional information. The members of the department, in particular Dr. R. Langendorf, contributed suggestions and criticisms in the preparation of this report.

1. Herrick, J. B.: Clinical Features of Sudden Obstruction of the Coronary Arteries, J. A. M. A. 59:2015 (Dec. 7) 1912.

In 529 patients the attack of myocardial infarction under study was their first one as far as could be determined; in the other 43 it was the second attack. Patients having more than two attacks were excluded from this series.

The data so analyzed were correlated with reports in the literature, and certain deductions were made to assist in the formulation of clinical guides, especially as to immediate prognosis. These are to be considered as tentative and subject to revision as larger series are analyzed.

SEX

There were 392 men (68.5 per cent) and 180 women (31.5 per cent); a ratio of 2.2:1. Only Hedley,² Bean,³ Rosenbaum and Levine⁴ and Rathe⁵ reported similar ratios. Most of the other observers⁶ had a higher ratio of men, varying from 13:1 (Parkinson and Bedford⁷) to

2. Hedley, O. F.: Five Years' Experience (1933-1937) with Mortality from Acute Coronary Occlusion in Philadelphia, *Ann. Int. Med.* **13**:598, 1939.

3. Bean, W. B.: Infarction of the Heart: Morphological and Clinical Appraisal of Three Hundred Cases; Predisposing and Precipitating Conditions, *Am. Heart J.* **14**:684, 1937.

4. Rosenbaum, F. F., and Levine, S. S.: Prognostic Value of Various Clinical and Electrocardiographic Features of Myocardial Infarction: I. Immediate Prognosis, *Arch. Int. Med.* **68**:913 (Nov.) 1944.

5. Rathe, H. W.: Myocardial Infarction: Clinical Features and Prognosis, *J. A. M. A.* **120**:99 (Sept. 12) 1942.

6. (a) White, P. D.: The Prognosis of Angina Pectoris and of Coronary Thrombosis, *J. A. M. A.* **87**:1525 (Nov. 6) 1926. (b) White, P. D., and Bland, E. F.: Further Report on the Prognosis of Angina Pectoris and of Coronary Thrombosis: A Study of Five Hundred Cases of the Former Condition and of Two Hundred Cases of the Latter, *Am. Heart J.* **7**:1, 1931. (c) Levine, S. A., and Brown, C. L.: Coronary Thrombosis: Its Various Clinical Features, *Medicine* **8**:245, 1929. (d) Willis, F. A.: Life Expectancy in Coronary Thrombosis, *J. A. M. A.* **106**:1890 (May 30) 1936. (e) Conner, L. A., and Holt, E.: The Subsequent Course and Prognosis in Coronary Thrombosis (An Analysis of Two Hundred and Eighty-Seven Cases), *Am. Heart J.* **5**:705, 1930. (f) Master, A. M.; Dack, S., and Jaffe, H. L.: Age, Sex and Hypertension in Myocardial Infarction Due to Coronary Occlusion, *Arch. Int. Med.* **64**:767 (Oct.) 1939. (g) Appelbaum, E., and Nicolson, G. H. B.: Occlusive Disease of the Coronary Arteries: An Analysis of the Pathological Anatomy in One Hundred and Sixty-Eight Cases with Electrocardiographic Correlation in Thirty-Six of These, *Am. Heart J.* **10**:662, 1935. (h) Goldsmith, G. A., and Willis, F. A.: Bodily Build and Heredity in Coronary Thrombosis, *Ann. Int. Med.* **10**:1181, 1937. (i) Wilhelmy, E. W., and Helwig, F. C.: Clinical and Pathologic Studies of Coronary Disease, *J. Missouri M. A.* **32**:476, 1935. (j) Fisher, R., and Zuckerman, M.: Coronary Thrombosis, *J. A. M. A.* **131**:385 (June 1) 1946. (k) Smith, C.; Sauls, C., and Ballew, J.: Coronary Occlusion: A Clinical Study of One Hundred Patients, *Ann. Int. Med.* **17**:681, 1942.

7. Parkinson, J., and Bedford, D. E.: Cardiac Infarction and Coronary Thrombosis, *Lancet* **1**:4, 1928.

3:1 (Mullins⁸). We have therefore confirmed the lesser incidence of myocardial infarction in women but not to the extent previously reported. Apparently the number of women having attacks of myocardial infarction is greater today than it was ten years ago. The cause of this increasing incidence of myocardial infarction in women is unanswered.

AGE

The youngest person in this series was 32 years of age and the oldest 84, and both were men. The average age of the entire group was 60.4 years, that of the women being 62.4 years while that of the men was 58.4 years. In table 1 is shown the distribution of the two sexes by decades. It will be seen that almost 75 per cent of the women had myocardial infarction between the ages of 50 and 70 years, with the greatest number in the seventh decade. About 62.5 per cent of the men had the attack between 50 and 70 years, with the largest number in the

TABLE 1.—*Age Distribution of Recent Myocardial Infarction in Men and Women by Decades*

Decade, Yr.	Men		Women		Total	
	No.	%	No.	%	No.	%
30 to 39.....	20	5.1	2	1.1	22	3.8
40 to 49.....	76	19.3	15	8.3	91	15.9
50 to 59.....	131	32.2	56	31.1	187	32.7
60 to 69.....	115	29.3	77	42.8	192	33.6
70 to 79.....	45	11.5	28	15.6	73	12.8
80 to 89.....	5	1.3	2	1.1	7	1.2
Total.....	392		180		572	

sixth decade. Almost identical results were obtained by other observers.⁹ Master and associates,^{6f} however, found infarction at a younger age, most of their patients falling in the period between 45 and 65 years.

MORTALITY DURING THE PATIENTS' STAY IN THE HOSPITAL

Of the 572 patients, 125 died during their stay in the hospital, for the most part within the first two weeks (table 2). This represents a mortality of 21.8 per cent. The mortality among the men was 18.6 per cent and among the women 28.9 per cent. Myocardial infarction thus has a greater rate of immediate fatalities in women than in men. The average age at death was 61.5 years; that of the women was 63.4 years, while that of the men was 59.6 years. The poor prognosis in women

8. Mullins, W. L.: Age Incidence and Mortality in Coronary Occlusion: A Review of Four Hundred Cases, *Pennsylvania M. J.* **39**:322, 1936.

9. (a) Howard, T.: Coronary Occlusion Based on Study of One Hundred and Sixty-Five Cases, *M. Times & Long Island M. J.* **62**:337, 1934. (b) Vander Veer, J. B., and Brown, L. E.: The Diagnosis and Prognosis of Coronary Occlusion: The Electrocardiogram as an Aid, *Pennsylvania M. J.* **39**:303, 1936.

has also been found by Willius^{6d} and Coombs.¹⁰ However, White and Bland^{6b} considered sex of no significance in mortality. The greater mortality rate in the women in this series may be due to the fact that they have a greater incidence of diabetes mellitus than do men. Women with myocardial infarction also have a greater frequency of thrombo-embolic phenomena and arrhythmia than do men and are older at the time of their attack. This will be discussed later. It must be emphasized that this analysis does not give the entire picture of immediate mortality, because many patients die before the physician sees them.

The immediate mortality rate in our series lies between the low mortality rates found by Master¹¹ (8 per cent), Mullins⁸ (9 per cent) and Conner and Holt^{6e} (16.2 per cent) and the higher mortality rates found by Cooksey¹² (39.6 per cent), Howard^{9a} (24 per cent), Rosenbaum and Levine⁴ (33 per cent) and Levine and Brown^{6c} (53 per cent). Analysis of our series shows that the immediate mortality rate increases with age, is greater with the second than with the first attack and is higher in those with a history of preexisting cardiac disease.

TABLE 2.—*Immediate Mortality from Recent Myocardial Infarction*

	Number of Cases	Percentage of Series	Average Age, Yr.	Number of Deaths	Mortality, %
Total.....	572	61.5	125	21.8
Men.....	392	68.5	59.6	73	18.6
Women.....	180	31.5	63.4	52	28.9

SEASONAL INCIDENCE

The seasonal incidence of myocardial infarction was discussed in 1926 by Bundesen and Falk¹³ and in 1927 by Cohn.¹⁴ Since then, numerous reports have appeared, all pointing to a lower incidence in summer. Master and associates¹⁵ did not consider that the difference in

10. Coombs, C. F.: Observations on the Etiological Correspondence Between Anginal Pain and Cardiac Infarction, *Quart. J. Med.* **23**:233, 1930.

11. Master, A. M.; Jaffe, H. L., and Dack, S.: The Treatment and Immediate Prognosis of Coronary Artery Thrombosis (Two Hundred and Sixty-Seven Attacks), *Am. Heart J.* **12**:549, 1936.

12. Cooksey, W. B.: Coronary Thrombosis: Follow-Up Studies with Special Reference to Prognosis, *J. A. M. A.* **104**:2063 (June 8) 1935.

13. Bundesen, H. N., and Falk, I. S.: Low Temperature, High Barometer and Sudden Death, *J. A. M. A.* **87**:1987 (Dec. 11) 1926.

14. Cohn, A. E.: Heart Disease from the Point of View of Public Health, *Am. Heart J.* **2**:275 and 386, 1927.

15. Master, A. M.; Dack, S., and Jaffe, H. L.: Factors and Events Associated with the Onset of Coronary Artery Thrombosis, *J. A. M. A.* **109**:546 (Aug. 21) 1937.

incidence which they observed was significant. Rosahn,¹⁶ recalculating Master's data, insisted that the difference was significant. Wolff and White¹⁷ and White,^{6a} reporting from Boston, observed that in most of their cases the condition occurred in the winter months. Wood and Hedley,¹⁸ reporting from Philadelphia, found a lower incidence in spring and summer than in the autumn and winter; they did not consider that this was due entirely to the fact that this was the season of summer vacations. Mullins,⁸ reporting from Pittsburgh, found about twice as many attacks during December, January and February as in the summer months. Bean,³ reporting from Boston, noted a low incidence in the summer and a slightly greater incidence in the spring than in the winter. Bean and Mills,¹⁹ reporting from Cincinnati, found the same decline in the summer months.

The data in our series are presented in table 3. It will be seen that there is a slight tendency for more attacks to occur in the winter

TABLE 3.—*Seasonal Incidence of Recent Myocardial Infarction*

Year	Jan.	Feb.	March	April	May	June	July	Aug.	Sept.	Oct.	Nov.	Dec.	Totals
1940	4	3	2	1	7	8	2	5	7	5	8	9	61
1941	13	11	10	10	8	7	5	6	9	7	6	7	99
1942	4	7	8	9	4	7	7	4	7	13	8	5	83
1943	8	7	3	7	7	11	8	8	9	2	17	6	93
1944	6	8	12	8	11	8	9	10	13	12	13	12	122
1945	12	9	7	7	6	6	10	12	10	12	9	14	114
Totals	47	45	42	42	43	47	41	45	55	51	61	53	572

months, but the disease in our patients does not follow a definite seasonal trend. There were more attacks in September than in December and January. There were as many attacks in June and August as in January and February. There were about the same number of attacks in March and April as in July. It must be recalled that our series was obtained during the war years, when vacations away from Chicago were rare. It is likely that the seasonal variation reported by others is to a large extent due to summer migration from the large communities on the part of susceptible persons. Seasonal incidence appears to be an unimportant factor as a precipitating cause of acute myocardial infarction.

16. Rosahn, P. D.: Incidence of Coronary Thrombosis in Relation to Climate, *J. A. M. A.* **109**:1294 (Oct. 16) 1937.

17. Wolff, L., and White, P. D.: Acute Coronary Occlusions: Report of Twenty-Three Autopsied Cases, Boston *M. & S. J.* **195**:13, 1926.

18. Wood, F. C., and Hedley, O. F.: Seasonal Incidence of Acute Coronary Occlusion in Philadelphia, *M. Clin. North America* **19**:151, 1935.

19. Bean, W. B., and Mills, C. A.: Coronary Occlusion: Heart Failure and Environmental Temperatures, *Am. Heart J.* **16**:701, 1938.

PRECIPITATING CAUSES

Considerable controversy has appeared in the literature concerning the precipitating causes of myocardial infarction. Many observers²⁰ insist that attacks are precipitated by unusual departures from the ordinary habits of the person. Included are unusual physical exertion and strain, overindulgence in sports, overeating, sexual excesses, emotional upsets, dreams and excessive travel. Occasionally, infections and post-operative states may appear as precipitating factors. The highest incidence of specific precipitating causes of myocardial infarction was reported by Rathe⁵ (20.8 per cent). Blumgart²¹ presented 11 patients of army personnel, varying in age from 26 to 56 years, with acute myocardial infarction consequent to strenuous exercise to which they were not accustomed. Riesman and Harris²² and Wolff and White,¹⁷ while agreeing that unusual departures from ordinary habits of living as well as infections may precipitate myocardial infarction, emphasized that many attacks occur while the patient is at rest or sitting or lying in bed. Herrick,²³ MacCollum²⁴ and Levine and Brown^{6c} denied that infections are precipitating factors. Parkinson and Bedford,⁷ Luten²⁵ and Master and associates¹⁵ stressed the fact that many persons are aroused from sleep by an attack of myocardial infarction. Phipps²⁶

20. Kahn, M. H.: Etiologic Factors in Angina Pectoris in Private Practice: Analysis of Eighty-Two Cases, *Am. J. M. Sc.* **172**:195, 1926. Fitzhugh, G., and Hamilton, B. E.: Coronary Occlusion and Fatal Angina Pectoris: Study of Immediate Causes and Prevention, *J. A. M. A.* **100**:475 (Feb. 18) 1933. Boas, E. P.: Coronary Occlusion as a Delayed Post-Operative Complication, *J. Mt. Sinai Hosp.* **3**:224, 1937. Campbell, S. B. B.: The Influence of Gall Bladder and Other Infections on the Incidence of Coronary Thrombosis, *Brit. Heart J.* **1**:781, 1936. Randall, D. S., and Orr, T. G.: Post-Operative Coronary Occlusion, *Ann. Surg.* **92**:1014, 1930. Menard, O. J., and Hurxthal, L. M.: Painless Coronary Thrombosis as a Post-Operative Complication, *S. Clin. North America* **11**:395, 1931. Paterson, J. C.: Relation of Physical Exertion and Emotion to Precipitation of Coronary Thrombosis, *J. A. M. A.* **112**:895 (March 11) 1939. Boas, E. P.: Angina Pectoris and Cardiac Infarction from Trauma or Unusual Effort with Consideration of Certain Medicolegal Aspects, *ibid.* **112**:1887 (May 13) 1939.

21. Blumgart, H. L.: The Relation of Effort to Attacks of Acute Myocardial Infarction, *J. A. M. A.* **128**:775 (July 14) 1945.

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23. Herrick, J. B.: The Coronary Artery in Health and Disease, *Am. Heart J.* **6**:589, 1931.

24. MacCollum, W. G., and Cowdry, E. V.: Arteriosclerosis: A Review of the Problem, New York, The Macmillan Company, 1933, p. 361.

25. Luten, D.: Contributory Factors in Coronary Occlusion, *Am. Heart J.* **7**:36, 1931.

26. Phipps, C.: Contributory Causes of Coronary Thrombosis, *J. A. M. A.* **106**:761 (March 7) 1936.

doubted the existence of any causal relationship between infections and undue activity and myocardial infarction. The most emphatic exponent of the lack of precipitating causes for myocardial infarction has been Master and his group.²⁷ They have emphasized this point in several of their publications.

In 50 of our cases (9.5 per cent) a possible precipitating cause was noted in the chart. This information is summarized in table 4. Eight of the patients had a preceding severe emotional trauma; 19 had infections of the upper respiratory tract, ranging from a sore throat, influenza or "head cold" to frank pneumonia. In 13 cases the disease occurred three to ten days postoperatively; 8 patients had histories of severe exertion, viz., straining at stool, effect of an enema, hurrying to an appointment, severe exercise, driving an automobile across country, delivering a speech, sexual intercourse and lifting a heavy object. One patient had upsetting dreams and another a history of an overdose of

TABLE 4.—*Precipitating Causes of Recent Myocardial Infarction **

	Number	Percentage
Cases in which there were no evident precipitating causes.....	474	90.5
Cases in which there were precipitating causes		
Severe emotion	8	1.5
Infections of the upper respiratory tract.....	19	3.6
Postoperative	13	2.5
Severe exertion	8	1.5
Other causes †	2	0.4
Total.....	50	9.5

* In other cases no information was available.

† In 1 case the condition occurred after an overdosage of insulin; in the other it followed a disturbing dream.

insulin prior to the myocardial infarction. While our results suggest that these factors played a part in precipitating an acute attack, it must be emphasized that the patients were 50 years of age or older and had preexisting evidence of cardiac disease. Apparently a trigger mechanism may be operative in precipitating acute myocardial infarction only with preexisting coronary disease.

Two sources of error in analyzing precipitating factors are present. One is the tendency of persons to seek for some unusual event whenever they become suddenly ill. The other is the fact that in our series we did not have the opportunity to question the patients personally and therefore had to rely on the record of the case. It is possible that had a personal survey been made without leading questions more pre-

27. Master, A. M.; Dack, S., and Jaffe, H. L.: (a) The Relation of Various Factors to the Onset of Coronary Artery Thrombosis, *J. Mt. Sinai Hosp.* 3:224, 1937; (b) The Precipitating Factors of Coronary Artery Occlusion, *Indust. Med.* 8:327, 1939; (c) The Relation of Effort and Trauma to Acute Coronary Occlusion, *ibid.* 9:359, 1940.

precipitating factors might have been revealed or some of the supposed precipitating factors might have turned out to be merely coincidental. Our study, while suggesting that some factors are of significance in precipitating the attack in at least a small proportion of cases, cannot be considered to have finally settled this highly controversial aspect of myocardial infarction. Nevertheless, it must be emphasized that in the vast majority of cases no precipitating cause was found. Apparently, then, recent myocardial infarction often cannot be prevented by the avoidance of undue activity. In planning long term activity of susceptible patients, this should be borne in mind and taboos kept at a minimum commensurate with common sense.

HYPERTENSION

"A preexisting hypertension is probably the most common etiologic factor in the development of myocardial infarction in the majority of cases" (Levine and Brown^{6c}). Allan²⁸ found a greater frequency of hypertension in patients with myocardial infarction than in the general population in the same age groups. The incidence of hypertension among patients with recent myocardial infarction is reported to vary between 28 per cent (Howard^{9a}) and 69 per cent (Master and associates²⁹). Thus, Parkinson and Bedford⁷ reported 49 per cent, Conner and Holt^{6e} 33.9 per cent, Levine and Brown^{6c} 40 per cent, Rosenbaum and Levine⁴ 57 per cent, Master and associates 62.4 per cent^{6f} and 66 per cent,¹¹ White and Bland^{6b} 34 per cent, Bean³ 49.3 per cent, Fisher and Zuckerman^{6j} 65.5 per cent, Smith and associates^{6k} 41 per cent and Rathe⁵ 63 per cent.

In our series a person was considered to be hypertensive if a definite history of hypertension was found recorded in his chart or was ascertained from his physician or if the patient had a persistent diastolic pressure of over 90 mm. of mercury during his stay in the hospital. In the majority the disease was diagnosed on the latter basis. There were 188 hypertensive patients, or 35.9 per cent, in our series (table 5). Among these, 28 had diabetes mellitus in addition. Our incidence may be lower than that reported by others because we excluded systolic hypertension unaccompanied by diastolic hypertension.

Hypertension occurred more often in the women (49.4 per cent) than in the men (29.7 per cent). This has been observed previously by others. The average age of the hypertensive patients was similar to that of the entire group. The immediate mortality rate of the hyper-

28. Allan, W.: The Relation of Arterial Hypertension to Angina Pectoris and Coronary Occlusion, *South. Med. & Surg.* 96:377, 1934.

29. Master, A. M.; Jaffe, H. L.; Dack, S., and Silver, N.: The Course of the Blood Pressure Before, During and After Coronary Occlusion, *Am. Heart J.* 26:92, 1943.

tensive group (table 5) corresponds closely to that of the entire series, and this is true of the mortality rates in the two sexes. Our findings suggest that hypertension has no influence on the immediate mortality in myocardial infarction. This is in agreement with the observations of many others³⁰ except those of Rosenbaum and Levine,⁴ who reported a 12 per cent greater mortality rate for their hypertensive than for their normotensive patients.

In agreement with Glendy, Levine and White,³¹ and Master and associates^{6f} we found a low incidence of hypertension in the younger patients (those between 32 and 36 years of age). In the older group, the incidence of hypertension increased with age, especially in the women.

DIABETES MELLITUS

It is well established that coronary sclerosis is common in diabetes mellitus. Nathanson³² observed coronary sclerosis in 41 of 100 cases of diabetes at necropsy. Joslin³³ found that patients with diabetes of five or

TABLE 5.—*Sex Distribution and Immediate Mortality in Hypertensive Patients with Recent Myocardial Infarction*

	Number	Percentage of Series	Average Age, Yr.	Number of Deaths	Mortality, %
Total.....	188	35.9	43	22.8
Men.....	107	29.7	59.0	18	16.8
Women.....	81	49.4	62.2	25	30.8

more years' duration almost always had coronary sclerosis. Many observers³⁴ have noted the great frequency of myocardial infarction in

30. White.^{6a} Levine and Brown.^{6c} Conner and Holt.^{6e} Master, Dack and Jaffe.^{6f} Fisher and Zuckerman.^{6j} Vander Veer and Brown.^{9b}

31. Glendy, R. E.; Levine, S. A., and White, P. D.: Coronary Disease in Youth, J. A. M. A. **109**:1775 (Nov. 27) 1937.

32. Nathanson, M. H.: Coronary Disease in One Hundred Autopsied Cases, Am. J. M. Sc. **183**:495, 1932.

33. Joslin, E. P.: Arteriosclerosis and Diabetes, Ann. Clin. Med. **5**:1061, 1927.

34. (a) Wilder, R. M.: Necropsy Findings in Diabetes, South. M. J. **19**:241, 1926. (b) Blotner, H.: Coronary Disease in Diabetes Mellitus, New England J. Med. **203**:709, 1930. (c) Root, H. F., and Sharkey, T. P.: Coronary Arteriosclerosis in Diabetes Mellitus, *ibid.* **215**:605, 1936. (d) Rabinowitch, I. M.: Arteriosclerosis in Diabetes, Ann. Int. Med. **8**:1436, 1935. (e) Joslin, E. P.; Root, H. F.; White, P. D., and Marble, A.: The Treatment of Diabetes Mellitus, Philadelphia, Lea & Febiger, 1937, p. 398. (f) Root, H. F.; Bland, F. E.; Gordon, W. H., and White, P. D.: Coronary Arteriosclerosis in Diabetes Mellitus: A Postmortem Study, J. A. M. A. **113**:27 (July 1) 1939. (g) Enklewitz, M.: Diabetes and Coronary Thrombosis: An Analysis of Cases Which Came to Necropsy, Am. Heart J. **9**:386, 1934. (h) Raab, A. P., and Rabinowitz, M. A.: Glycosuria and Hypoglycemia in Coronary Thrombosis, J. A. M. A. **106**:1705 (May 16) 1936,

diabetes. Enklewitz,^{34g} Master and associates,^{6f} Conner and Holt,^{6e} Bean,³ White and Bland^{6b} and Levine and Brown^{6c} reported that from 10 to 23.7 per cent of patients with acute myocardial infarction had diabetes. Levine and Brown^{6c} included patients with transient glycosuria in their series. This may explain why their reported incidence was higher than in other series. Master and associates^{6f} found that diabetes was commoner in women than in men and that its incidence increased with age. Levine and Brown^{6c} concluded that diabetes did not alter the prognosis of the attack or the age at which myocardial infarction occurred. Master and his associates^{6f} agreed that diabetes was not a factor in the occurrence of myocardial infarction in men and young women but expressed the opinion that it played a definite part in women over 50 years of age. Conner and Holt^{6e} concluded that diabetes in itself is not a predisposing cause of infarction. Saphir and associates³⁵ found that

TABLE 6.—*Sex Distribution of Recent Myocardial Infarction and Immediate Mortality in Patients with Diabetes with or without Ketosis*

	Number	Average Age, Yr.	Number of Deaths	Mortality, %	Number with Diabetic Ketosis	Number of Deaths with Diabetic Ketosis	Mortality in Patients with Diabetic Ketosis, %
Total.....	85	28	32.9	19	10	52.6
Men.....	36	59.2	10	27.8	6	2	33.3
Women.....	49	61.4	18	36.7	13	8	61.5

myocardial infarction was not as frequent in patients with diabetes as might be inferred from the literature.

In our series there were 85 patients with diabetes, or 16.2 per cent of the entire series (table 6). Of these, 28 had hypertension in addition. The average age of the patients with diabetes agreed with that of the whole series. There were 36 men and 49 women. The mortality rate for the men was 27.8 per cent and that for the women 36.7 per cent, as contrasted with 18 and 29 per cent for the whole series. Thus it will be seen that the mortality rate of persons with diabetes is greater than that of the whole group for both the men and the women. In contrast to hypertension, diabetes adds definitely to the gravity of the prognosis. The number of cases of diabetes combined with hypertension is too small for us to draw any specific conclusions about the gravity of this combination. Of the 85 patients with diabetes, 19 (22.4 per cent) had ketosis on their admission to the hospital, and 10 of the 19 died. Twenty-five others (29.4 per cent) were in a poorly controlled

35. Saphir, O.; Pfieft, W. S.; Hamburger, W. W., and Katz, L. N.: Coronary Arteriosclerosis: Coronary Thrombosis and the Resulting Myocardial Changes, *Am. Heart J.* 10:567 and 762, 1935.

diabetic state (the urine contained sugar [3 to 4 plus]). When the number of patients with uncontrolled diabetes and patients with ketosis is subtracted from the entire series of cases of diabetes, the mortality percentage falls within the range for the entire series. Diabetes definitely increases the mortality rate, primarily by leading to uncontrolled diabetic states after infarction. Patients with uncontrolled diabetes therefore require immediate and adequate therapy. As long as there is no ketosis and the fluid balance is maintained, it is perhaps safer not to use insulin. A high blood sugar level provides the optimum nutrition to the myocardium and prevents any dangerous hypoglycemic reactions and also any detrimental direct effect of insulin on the myocardium. More of the women than of the men had diabetes out of control on their admission to the hospital (table 6). It may be concluded from our series that diabetes adds to the gravity of the immediate prognosis, especially in women.

PERIARTERITIS NODOSA AND THROMBOANGIITIS OBLITERANS

On rare occasions, periarteritis nodosa³⁶ and thromboangiitis obliterans³⁷ lead to myocardial infarction. One case of periarteritis nodosa and 1 of thromboangiitis obliterans, in both of which the diagnosis was proved at necropsy, are included in our series.

SYPHILIS

Syphilis as an etiologic agent of myocardial infarction has been reported by many.³⁸ The incidence varies between 2.7 and 14.2 per cent. Levine and Brown^{6c} and White^{6a} stated that syphilis is a rare underlying factor in the production of myocardial infarction. Cole and Bohning³⁹ found 3 instances of myocardial infarction in 30 patients with cardiovascular syphilis at necropsy. Syphilis can narrow the coronary ostia and thereby lead to myocardial infarction. However, syphilis is

36. Logue, R. B., and Mullins, F.: Polyarteritis Nodosa: Report of Eleven Cases with a Review of Recent Literature, *Ann. Int. Med.* **24**:11, 1946.

37. Barron, M. E., and Linenthal, H.: Thromboangiitis Obliterans: General Distribution of the Disease, *Arch. Surg.* **19**:735 (Oct.) 1929. Samuels, S. S., and Feinberg, S. C.: The Heart in Thromboangiitis Obliterans, *Am. Heart J.* **6**:255, 1930. Greenfield, I.: Coronary Artery Thrombosis with Recovery in a Case of Thromboangiitis Obliterans, *ibid.* **22**:707, 1941. Fatherree, T. J., and Hines, E. A.: Vascular Clinics: IV. Fatal Complications of Thromboangiitis Obliterans; a Clinical Study, *Proc. Staff Meet., Mayo Clin.* **13**:342, 1938. Allen, E. V., and Willius, F. A.: Disease of the Coronary Arteries Associated with Thromboangiitis Obliterans of the Extremities, *Ann. Int. Med.* **3**:35, 1929.

38. Bean.³ White.^{6a} White and Bland.^{6b} Levine and Brown.^{6c} Conner and Holt.^{6e} Appelbaum and Nicolson.^{6g}

39. Cole, S. L., and Bohning, A.: Electrocardiographic Patterns in Cardiovascular Syphilis, *Am. J. M. Sc.* **207**:317, 1944.

often accompanied by coronary atherosclerosis, and it may be the latter which is responsible for the infarction.

In our series there were 4 possible instances of the disease, with only 2 verified at autopsy. Syphilis is a rare cause of myocardial infarction and was the possible etiologic factor in only 0.8 per cent of our series.

ANGINA PECTORIS

Angina pectoris prior to myocardial infarction has been reported as occurring in from 22.4 to 71.6 per cent of the cases.⁴⁰ In our series 382 patients, or 72.9 per cent, had angina pectoris prior to the attack (table 7). Angina pectoris was about equally common in the two sexes and occurred as often in those with anterior as in those with posterior myocardial infarction. The angina was described either as typical or (in 29 cases) as indigestion, stomach ache or heart burn. The mortality rate was 23.3 per cent for the men and 28 per cent for the women,

TABLE 7.—*Relation of Angina Pectoris to Recent Myocardial Infarction and Effect on Immediate Mortality*

	Anginal Attacks Prior to Infarction	No Angina Prior to Infarction	Anginal Attacks During Stay in Hospital Following Infarction	"Silent Coronary" *
Total number.....	382	138	69	18
Percentage of entire series.....	72.9	26.3	13.2	3.4
Number of deaths.....	95	29	27	5
Mortality rate of group, %.....	25.6	21.0	39.1	27.7

* "Silent coronary" or "silent infarction" is defined as a condition in which no preceding angina or pain occurred during the attack.

both figures only slightly higher than the mortality rate for the entire series. White,^{6a} Bedford,⁴¹ Rathe⁵ and Fisher and Zuckerman^{6j} expressed the opinion that the presence of angina pectoris prior to the attack had no influence on the immediate prognosis of myocardial infarction. Rosenbaum and Levine⁴ concluded that the patients with angina pectoris had a better prognosis than those without it. Our results indicate that preexisting angina pectoris had little, if any, effect on the prognosis of recent myocardial infarction.

In 138 patients (26.3 per cent) no attacks of angina pectoris occurred prior to the infarction (table 7). The mortality rate in this group was 21 per cent. The absence of preexisting angina, therefore, does not influence the immediate prognosis of myocardial infarction.

Angina pectoris continued or developed after the infarction while the patient remained in the hospital in 69 cases (13.2 per cent) in our

40. Bean,³ Rosenbaum and Levine.⁴ White.^{6a} White and Bland.^{6b} Willus.^{6d} Conner and Holt.^{6e} Parkinson and Bedford.⁷ Howard.^{9a}

41. Bedford, D. E.: Prognosis in Coronary Thrombosis, *Lancet* 1:223, 1935.

series (table 7). These patients remained in the hospital for six to eight weeks (up to ten weeks) and were in bed for the most part. The fact that 27 of these patients died (39.1 per cent) indicates that the persistence or development of angina after infarction makes the immediate prognosis graver. Fisher and Zuckerman⁶¹ and Master and others¹¹ found that patients with angina pectoris also had a much poorer prognosis after leaving the hospital, succumbing in many instances because of cardiac failure or another attack of myocardial infarction.

PAIN DURING THE ATTACK OF MYOCARDIAL INFARCTION

Many observers⁴² have reported instances in which the patient had no pain before or during the myocardial infarction. This has been called "silent coronary occlusion" or "silent myocardial infarction." The mortality rate among patients with silent infarction has been reported as small. In our series 18 patients had a silent myocardial infarction, with an immediate mortality rate of 27.7 per cent (table 7). This mortality rate is slightly higher than that for the entire series but is of doubtful significance. Saphir and associates³⁵ found that 13 of their 34 patients had no pain before or during infarction; they observed that congestive failure, debilitating disease or a clouded sensorium may explain the absence of pain in some cases. In our series one third (6 of 18) of the patients with "silent" infarction had congestive cardiac failure. Some observers have stressed that second attacks of myocardial infarction may be painless. In our series all the silent infarctions occurred during initial attacks.

Pain of various descriptions, including pain in the precordium, chest, left arm or epigastrium, occurred in 506 patients in this series at the time of the acute myocardial infarction. For the most part the pain was typical in character and location; but, in 18 patients the pain was atypical, according to its description and location. Some had pain only in the throat, neck, teeth, face, tongue or jaws or in a combination of these. Others had pain in the upper or lower part of the back. Several had pain in the right axilla or in the right half of the chest. Some had pain only in the abdomen and presented a difficult problem in ruling out the diagnosis of an acute surgical condition within the abdomen. One patient had only rectal tenesmus. Of the patients with

42. (a) Kennedy, J. A.: The Incidence of Myocardial Infarction Without Pain in Two Hundred Autopsied Cases, *Am. Heart J.* **14**:703, 1937. (b) Gross, H., and Engelberg, H.: A Comparison of the Hypertensive and Nonhypertensive Phases Following Coronary Thrombosis, *Am. J. M. Sc.* **199**:621, 1940. (c) Wearn, J. T.: Thrombosis of Coronary Arteries with Infarction of the Heart, *ibid.* **165**:250, 1923. (d) Gorham, L. W., and Martin, S. J.: Coronary Occlusion With and Without Pain: An Analysis of One Hundred Autopsied Cases with Reference to the Tension Factor in Cardiac Pain, *Arch. Int. Med.* **62**:821 (Nov.) 1938.

atypical pain, 4 died (22.2 per cent), which corresponds to the mortality rate for the entire series.

The typical pain was described as squeezing, pressure, burning and choking. The duration of pain was extremely variable, lasting anywhere from one to thirty-six hours. Saphir and associates³⁵ found that the duration and severity of the pain were unreliable guides in the diagnosis of acute myocardial infarction. The character and intensity of the pain, to a large extent, depend on the threshold for pain, and this varies from person to person (Libman⁴³). White^{6a} stated that the more severe the pain, the worse the prognosis. Rosenbaum and Levine⁴ and others observed that the severity of the pain, its location and its radiation had little prognostic value. We agree that the character, location, radiation and duration of the pain during the attack are of no prognostic significance.

BLOOD PRESSURE DURING AND AFTER ACUTE MYOCARDIAL INFARCTION

A fall in blood pressure following myocardial infarction has been reported by many observers.⁴⁴ These observers noted that the fall in pressure is greater in hypertensive persons than in the normotensive. In both groups systolic and diastolic pressures are affected, but the drop is greater in the systolic pressure, leading to a reduction in pulse pressure. Master and associates²⁹ called attention to the grave prognosis indicated when the pulse pressure was lower than 20 mm. of mercury. They also noted that in the majority of the cases the fall was rapid, reaching a minimum in one to three days; occasionally, however, the fall was slower, in some cases occupying one to two weeks. They emphasized that the hypertensive group tolerated the drop in blood pressure better than the normotensive group, even though the drop was greater in the former; in many hypertensive patients the blood pressure after it dropped was still at hypertensive levels. Middleton,⁴⁵ Fishberg,⁴⁶ Bedford⁴¹ and Rosenbaum and Levine⁴ found that when the systolic blood pressure was maintained at 80 mm. of mercury or less for hours and, especially, for days, the outlook became extremely unfavorable. Rathe⁵ emphasized that the prognosis was grave if the systolic pressure did not return to 100 mm of mercury within five days. Saphir and

43. Libman, E.: Observation on Individual Sensitiveness to Pain, *J. A. M. A.* **102**:335 (Feb. 3) 1934.

44. Rosenbaum and Levine.⁴ White.^{6a} Levine and Brown.^{6c} Conner and Holt.^{6e} Parkinson and Bedford.⁷ Wolff and White.¹⁷ Gross and Engelberg.^{42b}

45. Middleton, W. S.: The Prognosis and Treatment of Coronary Occlusion, *Minnesota M. J.* **18**:710, 1935.

46. Fishberg, A. M.: *Heart Failure*, ed. 2, Philadelphia, Lea & Febiger, 1940, p. 456.

associates,³³ Fishberg⁴⁶ and Master and associates²⁹ observed that occasionally the arterial blood pressure did not fall and at times there was an actual transitory rise.

In our study we observed that the blood pressure usually reached a minimum within twenty-four hours; in some cases, however, the drop continued for one to two weeks. The hypertensive group had a greater drop in blood pressure than the normotensive. The fall in diastolic pressure was less than in systolic. The diminished pulse pressure in itself proved of no prognostic significance unless it became 25 mm. of mercury or less. With such a small pulse pressure there was at least a 50 per cent mortality rate in our series. This is in accord with similar observations reported by Coombs.¹⁰ The degree of fall of systolic blood pressure, provided the pressure remained above 100 mm. of mercury, was of no prognostic significance. When the systolic blood pressure fell below 100 mm. of mercury in the hypertensive group and remained at these levels for three to five days, the prognosis was graver. We observed, further, that when the systolic blood pressure in any group was maintained at less than 90 mm. of mercury for several days the prognosis became extremely grave indeed.

Some of the hypertensive group continued to remain at the hypertensive level, although many had a drop in blood pressure. Actually we had information that a small number of patients in our series had a transitory rise in blood pressure at the time of the myocardial infarction. The cause for this temporary rise in blood pressure remains unanswered. Fishberg⁴⁶ suggested that it occurs when there is notable left ventricular failure and is a consequence of asphyxia, but many of our patients with temporary rises in blood pressure did not have decided failure of the left side of the heart. Levine and Ernstene⁴⁷ considered that pain alone is not the important stimulus for the elevation of blood pressure; we are inclined to agree with them. It is possible that the rise in pressure may be reflex in origin, resulting from stimulation of nerves in the heart, which may follow the infarction. Singer⁴⁸ has noted such a rise in pressure on stimulation of the nerves of the coronary vessels in the dog.

We do not agree with Levine and Brown^{6c} that the patients who show a pronounced fall in blood pressure with only a slight subsequent rise do best, because in our series many of these patients did poorly and died.

The 308 patients on whom data on blood pressure were available were divided into three groups according to their blood pressure on discharge from the hospital. In the first group we included all those

47. Levine, S. A., and Ernstene, A. C.: Observations on Arterial Blood Pressure During Attack of Angina Pectoris, *Am. Heart J.* 8:323, 1933.

48. Singer, R.: Experiments on Pain Sensitiveness of Heart and Large Blood Vessels and Its Relation to Angina Pectoris, *Wien. Arch. f. inn. Med.* 13:157, 1926.

who were admitted with a normal blood pressure and whose pressure remained normal during their stay in the hospital. In this group there were 144 patients; 35 of these had a history of hypertension. In the second group were those who were admitted with an elevated blood pressure and whose blood pressure on discharge from the hospital was within normal limits. There were 85 patients in this group, 78 of whom had a history of hypertension. In the third group were the patients who had an increased blood pressure on discharge. In this group there were 79 patients, 75 of whom had a history of hypertension. Thus in our series (table 8) 188 of the 308 patients had a history of hypertension. About three fourths of the patients had a normal blood pressure on discharge from the hospital, although four fifths of them had a definite history of hypertension. The remaining one fourth had hypertension on discharge. Of the known hypertensive patients, 84 (44.7 per cent) had a normal blood pressure on discharge after being hospitalized for an average of six to eight weeks.

TABLE 8.—*Immediate Mortality from Recent Myocardial Infarction in Relation to the Level of the Blood Pressure **

	Number	Percentage of Entire Series	Number of Deaths	Mortality Rate, %
Hypertensive blood pressure.....	188	35.9	43	22.9
Normotensive blood pressure.....	303	57.8	60	19.8
Shock level of blood pressure.....	36	6.9	28	77.8

* The criteria of separating the groups are discussed in the text.

Levine and Brown⁴⁶ and Master and others²⁰ observed that shock makes the prognosis worse. In our group of 524 patients, 36 had definite signs, symptoms and blood pressures indicative of shock. Of these, 28 died (table 8). This indicates conclusively that the presence of shock is associated with a poor prognosis. This high mortality rate among the patients in shock (77.8 per cent) contrasts with the mortality rate of 19.8 and 22.9 for the normotensive and the hypertensive group, respectively, not in shock.

The mechanism of the initial fall in blood pressure after infarction is still controversial. Fishberg⁴⁶ at first attributed it to peripheral circulatory failure and thought that it was reflex in origin, the reflex originating in the heart. However, Mendlowitz and associates⁴⁹ attributed it to forward failure arising dynamically because of the infarction in the left ventricle. The latter viewpoint was later concurred in by Fishberg⁴⁶ and by Stead.⁵⁰ We also consider that the fall in blood pressure

49. Mendlowitz, M.; Schauer, G., and Gross, L.: Hemodynamic Studies in Experimental Coronary Occlusion: II. Closed Chest Experiment, *Am. Heart J.* **13**:664, 1937.

50. Stead, E. A., and Ebert, R. V.: Shock Syndrome Produced by Failure of the Heart, *Arch. Int. Med.* **69**:369 (March) 1942.

is cardiogenic and due to a diminished cardiac output involving forward failure. This viewpoint as to the cardiogenic origin appears to be supported by the observations of Master and associates,²⁹ who found that around two thirds of the hypertensive patients had a return of their blood pressure to hypertensive levels within one to two years after the occurrence of the infarction.

LOCATION OF INFARCT

Criteria used for localizing infarcts are those established by one of us (L. N. K.).⁵¹ In this series there were 244 infarctions of the anterior and 160 of the posterior wall (table 9). In addition, there were 49 infarctions of the anteroseptal wall, 22 of the anterolateral wall, 34 of

TABLE 9.—*Distribution of Recent Infarction by Location as Determined by Electrocardiographic Contour*

Location	Total			Men			Women		
	No. in Group	No. of Deaths in Group	Immediate Mortality Rate, %	No. in Group	No. of Deaths in Group	Immediate Mortality Rate, %	No. in Group	No. of Deaths in Group	Immediate Mortality Rate, %
Anterior.....	244	43	17.6	159	28	17.6	85	15	17.6
Anteroseptal.....	49	20	40.8	36	12	33.0	13	8	61.5
Anterolateral.....	22	0	0.0	18	0	0.0	4	0	0.0
Posterior.....	160	37	23.1	110	20	18.2	50	17	34.0
Postero-septal.....	34	11	32.3	27	7	25.9	7	4	57.1
Postero-lateral.....	11	0	0.0	8	0	0.0	3	0	0.0
Atypical.....	26	8	30.8	18	4	22.2	8	4	50.0
Lateral.....	2	0	0.0	2	0	0.0	0	0	0.0
Combined *.....	24	6	25.0	14	2	14.3	10	4	40.0
Total.....	572	125	21.9	392	73	18.6	180	52	28.9

* Indicates posterior pattern in limb leads and anterior pattern in the chest leads.

the postero-septal wall and 11 of the postero-lateral wall. Twenty-six were atypical, 2 were lateral and 24 were combined (a posterior pattern in the limb leads and an anterior pattern in the chest leads). The mortality rate was greatest in the patients having infarcts involving the septum and in those having the atypical and combined varieties.

Vander Veer and Brown,⁵⁰ Stroud⁵² and Wood and associates⁵³ stated the belief that anterior infarction is far more serious than the variety involving the posterior wall. Master and associates,¹¹ Willius,^{6d}

51. Katz, L. N.: *Electrocardiography*, ed. 2, Philadelphia, Lea & Febiger, 1946, chap. 11, p. 280.

52. Stroud, W. B., in discussion on Levine, S. A., and Levine, H. D.: *Electrocardiographic Study of Lead IV, with Special Reference to Findings in Angina Pectoris*, Tr. A. Am. Physicians 50:303, 1935.

53. Wood, F. C.; Bellet, S.; McMillan, T. M., and Wolferth, C. C.: *The Electrocardiographic Study of Coronary Occlusion: Further Observations on the Use of the Chest Leads*, Arch. Int. Med. 52:752 (Nov.) 1933.

Barnes and Ball⁵⁴ and Levine and Brown⁵⁵ concluded that the mortality rate is the same in both anterior and posterior varieties. In our series we found the mortality rate to be 17.6 per cent among the patients with infarctions of the anterior wall and 23.1 per cent among those with infarctions of the posterior wall. The former is slightly below and the latter slightly above the average mortality rate. In all varieties except that involving the anterior wall the mortality rate was higher in the women than in the men. It would appear that there is little difference, by and large, in the immediate mortality rate among patients with infarctions of the anterior wall and those with infarctions of the posterior wall.

CARDIAC ARRHYTHMIA

In the consideration of cardiac arrhythmias we have excluded sinus tachycardia and intraventricular block from the general consideration. These will be considered separately in the following paragraphs.

Cardiac arrhythmias have been reported⁵⁵ to occur in myocardial infarctions in 9 to 27 per cent of the cases, with an average of 18 per cent. The most common arrhythmia reported was premature systoles of ventricular origin. These did not influence the immediate prognosis of myocardial infarction. Next in order of frequency was auricular fibrillation, with heart block and paroxysmal tachycardia following. Master and associates^{55a, b} emphasized that arrhythmias are more common in severely ill patients who have previous cardiac damage resulting from hypertension or previous myocardial infarction. Many of these patients in their series had enlarged hearts. They found that arrhythmias were more prone to develop in women than in men and that the frequency increased with age. Several observers have emphasized that persistence of an arrhythmia for any considerable period may be followed by cardiac failure. It has been noted that some arrhythmias seem to initiate myocardial infarction or at least are present at the start.

54. Barnes, A. R., and Ball, R. G.: The Incidence and Situation of Myocardial Infarction in One Thousand Consecutive Postmortem Examinations, *Am. J. M. Sc.* **183**:215, 1932.

55. (a) Master, A. M.; Dack, S., and Jaffe, H. L.: Partial and Complete Heart Block in Acute Coronary Artery Occlusion, *Am. J. M. Sc.* **196**:513, 1938; (b) Disturbances of Rate and Rhythm in Acute Coronary Artery Thrombosis; *Ann. Int. Med.* **11**:735, 1937. (c) Salcedo-Salgar, J., and White, P. D.: The Relationship of Heart Block, Auriculoventricular and Intraventricular to Clinical Manifestations of Coronary Disease, Angina Pectoris and Coronary Thrombosis, *Am. Heart J.* **10**:1067, 1935. (d) Askey, J. M., and Neurath, O.: The Prognostic Significance of Auricular Fibrillation in Association with Myocardial Infarction, *ibid.* **29**:575, 1945. (e) Meakins, J. C., and Eakin, W. W.: Coronary Thrombosis: A Clinical and Pathologic Study, *Canad. M. A. J.* **26**:18, 1932. (f) Schwartz, S. P.: Auriculoventricular Dissociation and Adams-Stokes Syndrome in Acute Coronary Vessel Closure, *Am. Heart J.* **11**:554, 1936.

Askey and Neurath^{55d} and Levine and Brown^{6c} observed that auricular fibrillation was the most serious arrhythmia. Appelbaum and Nicolson,^{6g} Schwartz,^{55f} Master and associates^{55a, b} and Rosenbaum and Levine⁴ stated the belief that heart block was the most serious. Master and associates^{55b} observed that most arrhythmias occurred in the first few days and were often transient. They emphasized that auricular fibrillation and paroxysmal tachycardia were usually transient, while heart block persisted for a longer time and in some cases became permanent.

In our series there were 94 instances of arrhythmia (16.4 per cent), excluding occasional premature systoles, sinus tachycardia and intra-

TABLE 10.—*Arrhythmias Occurring Following Recent Myocardial Infarction**

Type of Arrhythmia	Number	Percentage of Series	Number of Deaths During Stay in Hospital	Percentage of Deaths in Group
Auricular fibrillation	17	18.1	5	29.4
Auricular flutter	4	4.3	3	75.0
First degree auriculoventricular block.....	23	24.5	6	23.1
Second degree auriculoventricular block.....	11	11.7	6	54.6
Complete auriculoventricular block with idioventricular pacemaker below bundle bifurcation....	4	5.3	4	100.0
Complete auriculoventricular block with pacemaker above bundle bifurcation.....	1		1	
Sinoauricular block	3	3.2	0	0.0
Coronary nodal rhythm.....	5	5.3	1	20.0
Middle nodal rhythm.....	2	2.1	1	50.0
Supraventricular tachycardia	3	3.2	2	66.6
Ventricular tachycardia	5	5.3	3	60.0
Runs of auricular extrasystoles.....	5	5.3	1	20.0
Runs of ventricular extrasystoles.....	1	1.0	1	100.0
Auriculoventricular dissociation	3	3.2	2	66.6
Ventricular extrasystoles from two foci.....	1	1.0	1	100.0
Ventricular extrasystoles in pairs.....	1	1.0	0	0.0
Numerous ventricular extrasystoles.....	2	2.1	1	50.0
Numerous auricular extrasystoles.....	5	5.3	3	60.0
Frequent auricular and ventricular extrasystoles	3	3.2	0	0.0
Totals.....	94	41	43.6

* This table does not consider occasional premature systoles, sinus tachycardia or intra-ventricular block.

ventricular block (table 10). They occurred in 64 men, with an average age of 60.4 years, and in 30 women, with an average age of 68.1 years. Twenty-one of the men (32.8 per cent) and 20 of the women (66.7 per cent) died, a combined mortality rate of 43.6 per cent. Thus it would appear that arrhythmias occurred with equal frequency in both sexes but at a later age in the women and that the prognosis was grave in both sexes but particularly so in the women. Arrhythmia is therefore an extremely grave complication in myocardial infarction.

The most frequent of the arrhythmias was first degree auriculoventricular block, which occurred in 23 patients (24.5 per cent). Next in frequency was auricular fibrillation, which occurred in 17 patients (18.1 per cent). Partial or second degree block occurred in 11 patients (11.7 per cent). Ventricular tachycardia occurred in 5 patients, while

supraventricular tachycardia occurred in 3. Complete heart block occurred in 5 patients, auricular flutter in 4 and nodal rhythm in 7.

Patients with complete heart block or with runs of ventricular premature systoles had the poorest prognosis, with a mortality rate of 100 per cent. Patients with auricular flutter had a mortality rate of 75 per cent; those with supraventricular tachycardia, 66.6 per cent, and those with ventricular tachycardia, 60 per cent. Among patients with auricular fibrillation and first degree auriculoventricular block there was a much lower mortality rate, 29.4 per cent and 23.1 per cent respectively.

Fifty-nine of the 94 patients with arrhythmias received digitalis and/or quinidine, and 41 of them (68.1 per cent) died (table 11). Fifteen of the 30 patients who received digitalis died—a 50 per cent mortality rate. Seven of 17 of the patients who received quinidine died—a mortality rate of 41.2 per cent. Seven of 12 of the patients

TABLE 11.—*Comparison Between Therapy and Immediate Mortality of Patients with Arrhythmia Following Recent Myocardial Infarction*

	Number in Group	Number of Deaths in Group	Mortality Rate of Group, %
Untreated.....	35	12	34.3
Treated			
With digitalis alone.....	30	15	50.0
With quinidine alone.....	17	7	41.2
With both digitalis and quinidine.....	12	7	58.3
Total treated.....	59	29	49.2

who received both digitalis and quinidine died—a mortality rate of 58.2 per cent. Thirty-five of the 94 patients received no treatment, and 12 (34.3 per cent) died. Our results show no reduction in immediate mortality rate following the use of digitalis and quinidine; in fact, the mortality rate is apparently increased. The results support the contention of Master and associates^{55b} that quinidine and/or digitalis therapy of arrhythmias in myocardial infarction is dangerous, more so than the presence of an arrhythmia alone. The reason that so many of the patients received digitalis and/or quinidine was because they had cardiac failure besides the arrhythmia and it was felt that the arrhythmia contributed to the cardiac failure or at least was detrimental and so should be abolished. The influence of cardiac failure in itself on prognosis will be considered in the following text.

In our series there were 73 cases of occasional premature systoles (table 12), a lower frequency than is reported by other observers.⁵⁶ In 44 they were ventricular, in 26 they were auricular and in 3 they

56. Levine and Brown.^{6c} Master and associates.^{55b}

were nodal. There were 11 deaths (25 per cent) among the patients with the ventricular variety, 6 among those with the auricular variety (23.1 per cent) and no deaths among those with the nodal premature systoles. The average rate of death among patients with all varieties of premature systoles was 16.6 per cent for the men and 34.6 per cent for the women. These figures compare favorably with the mortality rate for the entire series. Apparently premature systoles when occurring occasionally are tolerated well by patients with myocardial infarction, at least as far as immediate mortality is concerned. By contrast,

TABLE 12.—*Sex Distribution and Immediate Mortality Rate of Patients with Occasional Premature Systoles Following Recent Myocardial Infarction*

Type	Group			Men			Women		
	Num- ber	Deaths	Mor- tality Rate, %	Num- ber	Deaths	Mor- tality Rate, %	Num- ber	Deaths	Mor- tality Rate, %
Ventricular.....	44	11	25.0	31	6	19.3	13	5	38.4
Auricular.....	26	6	23.1	14	2	14.2	12	4	33.3
Nodal.....	3	0	0.0	2	0	0.0	1	0	0.0
Total.....	73	17	23.3	47	8	16.6	26	9	34.6

TABLE 13.—*Occurrence of Intraventricular Block with Recent Myocardial Infarction*

Sex	No. in Group	Aver- age Age, Yr.	No. of Deaths in Group	Imme- diate Mor- tality Rate of Group, %	No. That Were Transi- tory	Location of Infarct				No. in Group with		
						Ante- rior	Pos- terior	Atypi- cal	Com- bined	Car- diac Fail- ure	Hyper- ten- sion	Both Hyper- tension and Cardiac Failure
Male	53	62.3	17	32.1	8	31	20	1	1	25	21	8
Female	19	61.3	10	52.6	3	8	9	1	1	12	7	5
Total	72	27	37.5	11	39	29	2	2	37	28	13

as pointed out previously, patients with runs of premature ventricular systoles had a mortality rate of 100 per cent.

INTRAVENTRICULAR BLOCK

Master and associates⁵⁷ observed that intraventricular block is usually evidence of severe cardiac disease. Patients with intraventricular block may have enlarged hearts, hypertension, previous myocardial infarcts and, frequently, heart failure. Master and his colleagues stressed the fact that intraventricular block is usually permanent and significant of septal involvement. In our series there were 72 cases of intra-

57. Master, A. M.; Dack, S., and Jaffe, H. L.: Bundle Branch and Intra-ventricular Block in Acute Coronary Artery Occlusion, *Am. Heart J.* 16:283, 1938.

ventricular block (table 13), or 12.5 per cent. It was found in all types of location of myocardial infarction. Fifty-three of the patients were men and 19 were women. Among the men there were 17 deaths (32.1 per cent) and among the women 10 deaths (52.6 per cent). Intraventricular block, therefore, increases the gravity of the prognosis. The block was transient in 11 instances.

Of the 72 patients with intraventricular block, 37 (51.4 per cent) had congestive heart failure, 28 (38.9 per cent) had hypertension and 13 (18.1 per cent) had both congestive heart failure and hypertension. The patients with persistent intraventricular block were those who were severely ill and had a history of either previous infarction or enlarged hearts with heart failure and hypertension. Our observations are in accord with those of Master and associates.⁵⁷

CONGESTIVE HEART FAILURE

Many observers⁵⁸ found that patients with myocardial infarction may exhibit signs and symptoms of congestive heart failure at the onset of the attack or during the first few days. Reports⁴⁶ have also appeared of the occasional occurrence of acute pulmonary edema or of sudden aggravation of preexisting heart failure as the only indication of myocardial infarction, particularly in Negroes.⁵⁹ In such patients there is usually reported to be some form of preexisting cardiac damage, due to hypertension, previous myocardial infarction or coronary sclerosis. Myocardial infarction involving a large area of the heart has been reported to be invariably accompanied with congestive heart failure. The incidence of congestive heart failure is found to increase with age. Master and associates⁵⁸ noted that congestive heart failure occurred with the same frequency in both sexes, but Rosenbaum and Levine⁴ found it to be slightly more common in women. Master and associates⁵⁸ and Levine and Brown⁶⁰ noted that three quarters of the patients with sinus tachycardia had congestive heart failure. As mentioned before, a prolonged arrhythmia can produce or aggravate congestive heart failure. Gross and Engelberg^{42b} reported a high incidence of congestive heart failure in their series (90 of 100 cases), but most observers have found a lower incidence than this. Fishberg,⁴⁶ Harrison⁶⁰ and Master and associates⁵⁸ observed that many patients with congestive cardiac failure associated with recent myocardial infarction are also in shock and

58. Master, A. M.; Dack, S., and Jaffe, H. L.: Coronary Thrombosis: An Investigation of Heart Failure and Other Factors in Its Course and Prognosis, *Am. Heart J.* **13**:330, 1937. See this reference for literature.

59. Hunter, W. S.: Coronary Occlusion in Negroes, *J. A. M. A.* **131**:12 (May 4) 1946.

60. Harrison, T. R.: *Failure of the Circulation*, Baltimore, Williams & Wilkins Company, 1935, pp. 316 and 328.

that in fatal cases the congestive failure usually predominates, except when death occurs early; in the latter instance shock predominates. All observers agree that congestive heart failure is of grave prognostic significance in patients with myocardial infarction.

In our series there were 121 instances (23.1 per cent) of congestive heart failure (table 14), usually of left-sided or combined heart failure. There were 65 men, or 17 per cent, with an average age of 61.3 years, and 56 women, or 31 per cent, with an average age of 69.1 years. Of the 65 men, 30 died (46.2 per cent), while 21 of the 56 women died (37.5 per cent), with an immediate mortality rate of 41.9 per cent for both sexes. The age of the men with congestive failure corresponds with that of the entire series, but the age of the women with failure is distinctly higher than the average for the women in the entire series. The frequency of congestive heart failure was greater in the women

TABLE 14.—*Immediate Mortality Rate in Congestive Heart Failure Complicating Recent Myocardial Infarction*

Sex	Number in Group	Average Age of Group, Yr.	Number of Deaths in Group	Mortality Rate of Group, %
Male.....	65	61.3	30	46.2
Female.....	56	69.1	21	37.5
Total.....	121	51	41.9
Without digitalis.....	20	4	20.0
With digitalis.....	101	47	46.5

than in the men. Our results confirm the impression that congestive failure is an extremely grave sign in both men and women but especially so in men. This is not unexpected, since the ordinary active older man has a greater level of activity than the ordinary active older woman. Rest in a man, therefore, is a greater departure from ordinary activity. Hence, when failure occurs when he is at rest it might be more ominous.

SINUS TACHYCARDIA

Sinus tachycardia in acute myocardial infarction has been stressed by some observers as a grave sign.⁶¹ In our series 116 patients (20.3 per cent) had sinus tachycardia (viz., a ventricular rate of over 100 in the first electrocardiogram—table 15). Of these, 79 were men, with an average age of 59.3 years, and 37 were women, with an average age of 62.4 years. Of these 116 patients, 65 died—a mortality rate of 57.1 per cent. Forty of the deaths occurred in men (50.6 per cent),

61. Levine and Brown.^{6c} Master and associates.⁵⁸

and 25 occurred in women (67.6 per cent). It is obvious, therefore, that sinus tachycardia is an exceedingly grave prognostic sign in both sexes.

Of the 116 patients with sinus tachycardia, 56 (48.2 per cent) had congestive heart failure, and 40 of the 56 died (71.4 per cent). The combination of tachycardia and congestive failure is of graver prognostic significance than either alone.

DIGITALIS IN CONGESTIVE HEART FAILURE

Of the 121 patients with heart failure, 101 received digitalis (table 14). Forty-seven of these patients died (a mortality rate of 46.5 per cent). Of the 20 patients with congestive heart failure who did not receive digitalis, only 4, or 20 per cent, died—a rate in agreement with the mortality rate in the entire series. It would appear from our observations that digitalis may be harmful when given to a patient with an acute myocardial infarct who has cardiac failure. As pointed out by Master and associates,⁵⁸ many of these patients are in

TABLE 15.—*Immediate Mortality Rate in Recent Myocardial Infarction Complicated by Sinus Tachycardia **

Sex	Number in Group	Average Age of Group, in Years	Number of Deaths in Group	Mortality Rate in Group, %
Male.....	79	59.3	40	50.6
Female.....	37	62.4	25	67.6
Total.....	116	65	57.1

* Determined by a sinus rate over 100 in the first electrocardiogram following infarction.

shock, a definite contraindication to the use of digitalis. It is possible that the difference in the mortality incidence attributed to the use of digitalis may be, in part at least, due to the graver state of the patient receiving this drug. Despite the risk, we believe that digitalis should be given when there are clear signs and symptoms of progressive heart failure and that the patients should be digitalized slowly. If acute pulmonary edema is present, the patient should be digitalized more rapidly. The criteria establishing the presence of congestive heart failure consist of persistent dyspnea, cyanosis and, especially, rales in the bases of the lungs. However, the diagnosis of pneumonia, which can give similar signs and symptoms, must be excluded. It is likely that the number of deaths due to myocardial infarction might be greatly decreased if digitalis were not so indiscriminately employed. There is perhaps a tendency to administer digitalis too rapidly in mild, transient and nonprogressive congestive failure. Evidences of forward failure and, especially, the appearance of shock are to be considered definite contraindications to the exhibition of digitalis.

THROMBOEMBOLIC PHENOMENA

Thromboembolic phenomena have been recorded by many observers.⁶² Parkinson and Bedford⁷ emphasized that involvement of the intraventricular septum in myocardial infarction may cause thrombosis of both ventricles, leading to pulmonary and systemic emboli. Nay and Barnes^{62d} observed that the emboli arising from the left side of the heart are found most often in the spleen, kidney and brain and less commonly in the mesenteric vessels and the vessels of the extremities. Blumer^{62b} expressed the opinion that some of the arterial occlusions may be the result of thrombosis, coincident with or subsequent to the myocardial infarction. Bean³ and Rosenbaum and Levine⁴ emphasized that most pulmonary emboli arise from veins of the pelvis and the extremities and that pulmonary occlusion, to a lesser extent, may arise from local thrombosis of the pulmonary vessels. Levine and Brown^{6c} observed that many instances of hemiplegia are due to emboli arising from the heart following acute myocardial infarction. Dozzi^{62c} found that 29 per cent of patients with myocardial infarction had cerebral thrombosis or embolism at necropsy. Askey and Neurath^{62e} stressed the fact that emboli may arise in the heart during auricular fibrillation. Garvin,^{62f} in a series of autopsies, found that thrombosis of the auricles was a frequent occurrence and may be the source of emboli. Nay and Barnes^{62d} noted that the majority of pulmonary emboli occurred when the blood pressure was low and when the patient had enforced rest in bed, with lack of movement of the extremities. These factors contribute to the formation of phlebothrombosis of the extremities, which in turn is the most frequent cause of pulmonary emboli. All observers agreed that emboli and thrombotic phenomena were of grave prognostic significance in patients with acute myocardial infarction.

In our series there were 52 patients (9.9 per cent) with embolic and thrombotic phenomena (table 16), and 29 of these patients died, a mor-

62. (a) Harrington, A. W., and Wright, J. H.: Cardiac Infarction: A Study of One Hundred and Forty-Eight Cases, *Glasgow M. J.* **119**:1, 1933. (b) Blumer, G.: The Importance of Embolism as a Complication of Cardiac Infarction, *Ann. Int. Med.* **11**:499, 1937. (c) Dozzi, D. L.: Cerebral Embolism as a Complication of Coronary Thrombosis, *Am. J. M. Sc.* **194**:824, 1937. (d) Nay, R. M., and Barnes, A. R.: Incidence of Embolic or Thrombotic Processes During the Immediate Convalescence from Acute Myocardial Infarction, *Am. Heart J.* **30**:65, 1945. (e) Askey, J. M., and Neurath, O.: The Treatment of Auricular Fibrillation Occurring with Myocardial Infarction, *ibid.* **30**:253, 1945. (f) Garvin, C. F.: Infarction in Heart Disease, *Am. J. M. Sc.* **203**:473, 1942. (g) Macht, D. I.: Experimental Studies on Heparin and Its Influence on Toxicity of Digitaloids, Congo Red, Cobra Venom and Other Drugs, *Ann. Int. Med.* **18**:772, 1943. (h) de Takats, G.; Trump, R. A., and Gilbert, N. C.: The Effect of Digitalis on the Clotting Mechanism, *J. A. M. A.* **125**:840, 1944. (i) Massie, E.; Stillerman, H. G.; Wright, C. S., and Minnick, V.: Effect of Digitalis Administration on the Coagulability of Human Blood, *Proc. Central Soc. Clin. Research* **16**:45, 1943.

tality rate of 55.8 per cent. There were 26 instances of pulmonary emboli, with 14 deaths (53.8 per cent). There were 11 instances of cerebral emboli, with 9 deaths (81.8 per cent). Two patients had both cerebral and pulmonary emboli, and they died. There was only 1 patient who had a fatal mesenteric thrombosis. The remainder had various peripheral emboli involving the lower extremities, kidneys and spleen. There was 1 instance of thrombophlebitis and 1 of recognized phlebothrombosis with pulmonary emboli; both of the patients survived. Our experience, in agreement with that of others, indicates that throm-

TABLE 16.—*Location of Thromboembolic Phenomena Following Recent Myocardial Infarction and Immediate Mortality Rate*

Location	Number in Group	Number of Deaths in Group	Percentage of Deaths in Group
Pulmonary.....	26	14	53.8
Cerebral.....	11	9	81.8
Cerebral and pulmonary.....	2	2	100.0
Femoral.....	3	1	33.3
Iliac.....	1	0	0.0
Popliteal.....	2	1	50.0
Renal.....	1	0	0.0
Pulmonary and renal.....	1	0	0.0
Splenic and pulmonary.....	1	0	0.0
Splenic and renal.....	1	1	100.0
Mesenteric.....	1	1	100.0
Thrombophlebitis of leg.....	1	0	0.0
Pulmonary and popliteal phlebothrombosis..	1	0	0.0
Total.....	52	29	55.8

TABLE 17.—*Immediate Mortality Rate of Patients with Thromboembolic Phenomena Complicating Recent Myocardial Infarction with and without Digitalis Therapy*

	Number in Group	Number of Deaths in Group	Mortality Rate in Group, %
Total.....	52	29	55.8
Receiving digitalis.....	20	16	80.0
Not receiving digitalis.....	32	13	40.6

boembolic phenomena occurring during recent myocardial infarction are of grave prognostic significance in both sexes. Cerebral and pulmonary emboli were the most dangerous.

Of the patients who had thromboembolic phenomena, 20 received digitalis. Sixteen of these died—a mortality rate of 80 per cent (table 17). Of the 32 other patients who received no digitalis, 13 died—a mortality rate of 40.6 per cent. It is thus apparent from our results that the occurrence of thromboembolic phenomena in patients receiving digitalis is more serious than in those without such medication. In part, this may be due to the fact that the treated patients were the more seriously ill. It is possible that the use of digitalis may actually help

to bring about thrombosis and emboli. Macht,^{62s} in assaying the use of digitalis in cats, found that it shortened the coagulation time. This effect was also found with ouabain. He concluded that under certain conditions digitalis promotes intravascular clotting and predisposes to thromboembolic phenomena. De Takats and others^{62h} reported a diminished effect of heparin in both human beings and dogs in the presence of digitalis. This has been confirmed by Massie and his colleagues⁶²ⁱ but has been questioned by others. We believe that the possibility that the use of digitalis does abbreviate coagulation time has not been excluded. On this account digitalis might be considered a dangerous drug in patients with myocardial infarction, and the indications for its use must therefore be clear in recent myocardial infarction before it is given. The use of heparin to neutralize this apparent tendency should be investigated. The real hazard in the use of digitalis, however, resides in its tendency to lead to ventricular fibrillation, a potential hazard already existing in every case of acute myocardial infarction.

Because of the serious prognosis attached to the occurrence of thromboembolic phenomena in recent myocardial infarction it is imperative that careful observation and good nursing care be employed for all patients prophylactically. Especially, care should be taken to prevent the occurrence of phlebothrombosis in the deep veins of the leg. When these phenomena occur, treatment must be instituted immediately. Ligation of the femoral vein should be considered if the emboli originate in the veins of the lower extremities, and heparin and/or Dicumarol should be given. When the emboli arise higher in the veins of the leg and when the site of origin is not definitely located, ligation of the inferior vena cava may be employed. If cerebral and intra-abdominal emboli occur, anticoagulant therapy must be administered as soon as possible, in addition to other measures. All who receive anticoagulation therapy should have frequent determinations of clotting time when heparin is used, or of prothrombin time when Dicumarol is used. We are not prepared to state that every patient with myocardial infarction should receive prophylactic anticoagulant therapy, as suggested by Peters and others,⁶³ until such time as this work has been confirmed in a larger series of cases.

PERICARDITIS

Pericarditis complicating acute myocardial infarction has been reported by many observers.⁶⁴ It ranged in frequency from 13.8 per

63. Peters, H. R.; Guyther, J. R., and Brambel, E. C.: Dicumarol in Acute Coronary Thrombosis, *J. A. M. A.* **130**:398 (Feb. 16) 1946.

64. Stewart, C. F., and Turner, K. B.: A Note on Pericardial Involvement in Coronary Thrombosis, *Am. Heart J.* **15**:232, 1938.

cent (Levine and Brown^{6c}) to 48 per cent (Wolff and White¹⁷). When the process of infarction extends to the visceral pericardium, pericarditis will develop. When this area is small, no friction rub may be audible even though pericarditis is present. A pericardial rub may not be audible when the infarct involves the posterior surface of the heart unless the subepicardial area is large or spreads to the anterior wall. Saphir and associates³⁵ emphasized that an audible friction rub does not always indicate involvement of the anterior wall since several of their patients showed involvement of the posterior wall. White^{6a} observed that pericarditis was found more frequently in patients who died than in those who survived.

In our series, pericarditis was noted clinically in 26 patients. Only in 15 of these was it verified by the electrocardiogram (which is specific only in acute diffuse pericarditis). It is likely that in many other cases the condition was missed on auscultation, because the rub is transitory and ordinarily not loud. Of the 26 patients with pericarditis, 5 died (19.2 per cent). Although our series of cases of pericarditis is small, it suggests that pericarditis is of little prognostic significance in recent myocardial infarction. It is possible, however, that when pericardial involvement is diffuse, suggesting an extensive infarct, it indicates a poor prognosis. In none of our cases was there evidence of pericardial effusion.

PNEUMONIA

Rosenbaum and Levine⁴ emphasized that advanced age and forced rest in bed, pulmonary congestion or the use of narcotics may lead to the development of pneumonia. In their series the incidence of pneumonia complicating myocardial infarction was 9 per cent, with a mortality rate of 89 per cent. In our series 52 patients (9.9 per cent) contracted pneumonia, and of these 30 died—a mortality rate of 57.7 per cent. We agree, therefore, with Rosenbaum and Levine that pneumonia is a grave prognostic sign when it complicates acute myocardial infarction. Penicillin should be given as soon as signs and symptoms of pneumonia become apparent.

GLYCOSURIA

Glycosuria has been reported frequently in the literature as a sequela of acute myocardial infarction. Levine and Brown^{6c} expressed the belief that it was produced by pain and fear during the acute episodes and was not necessarily indicative of diabetes mellitus. Edelmann⁶⁵ thought that myocardial infarction caused latent diabetes to become

65. Edelmann, A.: Ueber die Bedeutung der Glykosurie und Hyperglykämie bei Erkrankungen der Koronararterien, *Wien. klin. Wchnschr.* 47:165, 1934.

manifest. Eppinger⁶⁶ attributed the glycosuria to the absorption of the products of protein destruction which favored an outpouring of epinephrine. Raab and Rabinowitz^{34h} found abnormal dextrose tolerance curves soon after the acute attack of myocardial infarction, which later became normal. They therefore argued that this was opposed to the existence of a latent diabetes.

In our series we found only 10 instances of glycosuria. This low incidence of glycosuria is probably due to the fact that specimens of urine were not available immediately after the attack. Some of our patients were not admitted to the hospital on the day of the attack; some were admitted as late as several days to two weeks afterward. Furthermore, most of the specimens of urine were examined twenty-four to forty-eight hours after the patient's admission. Since glycosuria is a transitory phenomenon, this may account for the small incidence in our series. It is possible to explain the transient glycosuria as a sequel to pain, fear and apprehension, which tend to release epinephrine, or it may be an expression of a poor circulation through the liver; it is known that ischemia of the liver leads to glycosuria. Vogt⁶⁷ has shown that glycosuria persisting over several days in the absence of diabetes mellitus may be due to the effect of epinephrine on the adrenal cortex.

OBSERVATIONS AT AUTOPSY

Of the 125 patients who died, necropsy was permitted on 46. Among the unusual conditions noted were cardiac aneurysms (8 cases) occurring either in old or recent myocardial infarcts.⁶⁸ Rupture of the heart occurred in 5 patients and was accompanied by a hemopericardium in each instance. In most cases of partial and complete auriculoventricular block complicating myocardial infarction, the infarct was located on the posterior surface of the left ventricle. In only 2 instances, 1 of a partial and 1 of a complete auriculoventricular block, was there involvement of the anterior surface of the left ventricle without involvement of the posterior wall.

Most of the patients with intraventricular block showed evidence of old fibrosis in the septum and of chronic heart disease of arteriosclerotic origin, or else they showed involvement of the septum by the acute myocardial infarction.

The locations of the infarct as shown in the electrocardiograms were in most instances confirmed by autopsy. This has been discussed in

66. Eppinger, H.: Die Coronarthrombose, *Wien. klin. Wchnschr.* **47**:210, 1934.

67. Vogt, M.: The Effect of Chronic Administration of Adrenaline on the Suprarenal Cortex and the Comparison of This Effect with That of Hexoestrol, *J. Physiol.* **104**:60, 1945.

68. Dr. Otto Saphir, of the Department of Pathology, permitted us to examine the files of his department.

detail recently by Katz, Feldman and Langendorf.⁶⁹ Occasionally postmortem examination revealed evidence of more extensive involvement of the heart than was suspected from the electrocardiogram.

SUMMARY AND CONCLUSIONS

1. A series of 572 cases of recent myocardial infarction observed at the Michael Reese Hospital in the years 1940 to 1945 inclusive has been studied, particularly in regard to the factors involved in causing immediate mortality. The figures for the mortality are based on deaths occurring during the patients' stay in the hospital. Most of the patients were Jews, and a few were Negroes.

2. Acute myocardial infarction occurs less frequently in women than in men. In women the infarction occurs, on the average, four years later than in men. The greatest frequency of infarction in women is in the seventh decade; men have the greatest frequency of infarction in the sixth decade. The women were, on the average, 3.8 years older than the men at the time of death. Women have a greater immediate mortality rate than men. This appears to be due to the greater incidence of diabetes mellitus, thromboembolic phenomena and arrhythmias in women than in men and to their older age at the time of the attack.

3. No definite seasonal incidence was observed. The period of this study covered the war years, when vacations away from Chicago were rare. Seasonal incidence appears to be an unimportant factor in a consideration of the precipitating cause of myocardial infarction.

4. In a small number of cases precipitating factors such as severe emotion, undue exertion, infection and postoperative states are significant in precipitating myocardial infarction. In this series there were such apparent precipitating factors in 9.5 per cent of the cases. In the remaining 90.5 per cent, no apparent precipitating factor was revealed. In the vast majority of cases myocardial infarction develops without undue stress, even occurring when the patient is in bed.

5. Hypertension occurred in 35.9 per cent of this series. The incidence increased with age, especially in the women, and the condition was rare in the younger group. Hypertension appears to have no influence on the immediate prognosis of acute myocardial infarction.

6. Diabetes mellitus, in contrast to hypertension, adds gravity to the immediate prognosis in both sexes, especially in women. It increases the frequency of death by precipitating uncontrolled diabetes and ketosis. Patients with uncontrolled diabetes and ketosis should receive immediate and adequate therapy. As long as there is no ketosis and the balance

69. Katz, L. N.; Feldman, D., and Langendorf, R.: The Diagnostic Value of Electrocardiographic Patterns Based on an Assay of Two Hundred and Sixty-One Additional Autopsied Cases, Proc. Internat. Am. Cardiac Cong., to be published.

of fluid is adequate, it is perhaps wise not to give insulin. A high blood sugar level appears to be advantageous.

7. Periarteritis nodosa, thromboangiitis obliterans and syphilis are rare causes of myocardial infarction.

8. Angina pectoris preceding the acute infarction was equally common in the two sexes. It has no significant effect on the immediate prognosis. The persistence of anginal pain after the acute attack makes the immediate prognosis graver.

9. The character, location, radiation and duration of the pain appear to have no prognostic significance in acute myocardial infarction. Silent infarctions are no more serious than those with pain.

10. The hypertensive group had a greater drop in blood pressure than the normotensive group following the appearance of the acute infarct. The pulse pressure fell in all groups. Pulse pressures of 25 mm. of mercury or less are of grave prognostic significance. The degree of fall of systolic blood pressures, provided the pressure remains above 100 mm. of mercury, is of no immediate significance. In the hypertensive group a fall in blood pressure to below 100 mm. of mercury for three to five days makes the immediate prognosis poor. In any group a blood pressure of 90 mm. of mercury for several days indicates a poor prognosis. The presence of shock in myocardial infarction is indicative of a poor immediate prognosis. A small number of patients actually have a transitory rise in blood pressure at the time of the acute attack. About two thirds of the patients on discharge from the hospital (usually after six to eight weeks) had a normal blood pressure, irrespective of the fact that many of them had a definite history of hypertension preceding the attack. The remaining one third had hypertensive blood pressures on discharge. The majority of these were known hypertensive patients.

11. The immediate mortality rate in patients with acute myocardial infarction was greatest in those having infarcts involving the septum and in those with the atypical and combined varieties. In all types of infarction except that of the anterior wall, the mortality rate was higher in the women than in the men. There were no statistically significant differences in the mortality rate among patients with infarctions of the anterior wall and those with infarctions of the posterior wall.

12. Cardiac arrhythmias occur in both sexes but at a later age in women. The immediate prognosis is grave in both sexes but particularly so in women. Quinidine and/or digitalis therapy for arrhythmias in acute myocardial infarction is not without hazard, the mortality rate being greater than with the arrhythmia alone. Premature systoles when occurring occasionally have no prognostic significance. However, in patients with runs of ventricular premature systoles there was a

mortality rate of 100 per cent. Intraventricular block increases the gravity of the immediate prognosis. Sinus tachycardia is a grave prognostic sign in both sexes.

13. Congestive heart failure is an extremely grave prognostic sign in both sexes, especially in men. The combination of sinus tachycardia and congestive heart failure is of graver prognostic significance than either alone. The age of women with congestive heart failure is distinctly higher than that of men.

14. Digitalis may be harmful when given to patients who have congestive heart failure complicating acute myocardial infarction. Those who received digitalis were sicker patients, and the high figures for mortality with the use of digitalis probably may be due to the graver state of the patient. Digitalis should be given only when there are clearcut signs and symptoms of progressive heart failure, and then the patients should be digitalized slowly. If acute pulmonary edema is present, digitalization should be more rapid. Patients with equivocal congestive heart failure and those with evidence of forward failure, especially the appearance of shock, should not be given digitalis. Digitalis administered prior to or during thromboembolic phenomena increases the immediate mortality rate. Digitalis appears to shorten the coagulation time, and this increases the hazard of its use in patients with acute myocardial infarction. Its real danger, however, is in the risk of inducing ventricular fibrillation.

15. Thromboembolic phenomena occurring during recent myocardial infarction even when digitalis is not exhibited are of grave prognostic significance in both sexes. Pulmonary and cerebral emboli are the most dangerous. On this account, thromboembolic phenomena require immediate treatment and prophylaxis.

16. Pericarditis complicating acute myocardial infarction is of no immediate prognostic significance. Pneumonia is a grave prognostic sign when it complicates acute myocardial infarction; for this reason penicillin should be given promptly when pneumonia appears. Glycosuria in patients without diabetes was infrequent.

17. It is concluded that studies such as this on even larger groups could help to define more clearly the natural history of acute myocardial infarction and reveal the factors which contribute to the determination of the immediate prognosis. The analysis made in this report, when correlated with similar studies in the past, shows definite trends which should be useful in evaluating management and prognosis in acute myocardial infarction.

CARDIAC OUTPUT IN MAN

An Analysis of the Mechanisms Varying the Cardiac Output Based on
Recent Clinical Studies

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CURRENT medical teaching regarding the factors controlling the cardiac output is based mainly on the concepts of animal physiology. When applied to man these concepts have of necessity been rather vague and sketchy. The advent of the foreign gas methods,¹ and, more recently, the wider use of the ballistocardiograph² and the method of catheterization of the right side of the heart³ now enable clinicians to investigate the output of the heart by actual measurement. The physician may now add knowledge gained from studies on man to that obtained by the physiologists in laboratory work on animals. With the accumulation of these observations, a reevaluation of the factors controlling the cardiac output in human beings appears to be in order. As might be expected, many factors affecting the cardiac output in man, with his intact nervous and circulatory systems, were not apparent in the conventional heart-lung preparation. The pur-

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1. (a) Starr, I., Jr., and Gamble, C. J.: An Improved Method for the Determination of Cardiac Output in Man by Means of Ethyl Iodide, *Am. J. Physiol.* **87**:450-473 (Dec.) 1928. (b) Grollman, A.: *The Cardiac Output of Man in Health and Disease*, Springfield, Ill., Charles C Thomas, Publisher, 1932.

2. (a) Starr, I.; Rawson, A. J.; Schroeder, H. A., and Joseph, N. R.: Studies on the Estimation of Cardiac Output in Man, and of Abnormalities in Cardiac Function, from the Heart's Recoil and the Blood's Impacts: The Ballistocardiogram, *Am. J. Physiol.* **127**:1-28 (Aug.) 1939. (b) Nickerson, J. L., and Curtis, H. J.: The Design of the Ballistocardiograph, *ibid.* **142**:1-11 (Aug.) 1944.

3. (a) Cournand, A.; Riley, R. L.; Breed, W. S.; Baldwin, E. de F., and Richards, D. W., Jr.: The Measurement of Cardiac Output in Man Using the Technic of Catheterization of the Right Auricle or Ventricle, *J. Clin. Investigation* **24**:106-116 (Jan.) 1945. (b) McMichael, J., and Sharpey-Schafer, E. P.: Cardiac Output in Man by a Direct Fick Method, *Brit. Heart J.* **6**:33-40 (Jan.) 1944. (c) Stead, E. A., Jr.; Warren, J. V.; Merrill, A. J., and Brannon, E. S.: The Cardiac Output in Male Subjects as Measured by the Technique of Right Atrial Catheterization: Normal Values with Observations on the Effect of Anxiety and Tilting, *J. Clin. Investigation* **24**:326-331 (May) 1945.

pose of this paper is to bring together these new data which appear to throw light on the mechanisms controlling the cardiac output in man.

On theoretic consideration, variations in the cardiac output might result from variation either in the heart rate or in the stroke volume. Variations in rate, however, appear to play a relatively minor role. Even patients with complete heart block and a constantly low heart rate are able to carry on a normal amount of activity and vary their cardiac outputs to meet circulatory demands of an active life.

An understanding of the mechanisms controlling the cardiac output, therefore, becomes a matter of discovering the factors determining the size of the stroke volume. A change in stroke volume may be produced either by altering the degree of diastolic filling, or by varying the amount of residual blood left in the ventricle at the end of systole or by a combination of these factors. The degree of ventricular filling theoretically could be changed by alteration in the filling pressure (atrial pressure) or by variations in the degree of diastolic relaxation of the ventricles. Changes in the completeness of ventricular emptying could cause considerable change in stroke volume.

METHODS

It is not the purpose of this communication to discuss the validity of the several methods of determining the cardiac output in man. This problem has recently been reviewed by Hamilton.⁴ In all the original observations reported here the cardiac output was determined by the method of catheterization of the right side of the heart, the direct Fick principle being utilized, or by the ballistocardiograph. Although the underlying principles of the former method are subject to little criticism, there are many practical problems associated with the technic which may lead to rather large errors in any single determination. In an analysis of some of these difficulties as experienced in over five hundred catheterizations in this clinic, it was concluded that the errors tended to be random and not systematic.⁵ A single determination of cardiac output might, therefore, be erroneous, but the results of a series of observations were much less likely to lead to faulty conclusions.

The critically damped, low frequency ballistocardiograph was used in some of the studies reported here.⁶ The ballistic method is particularly useful in the study of rapid variations in the cardiac output. In addition, observations may be made many times on the same subjects. Calculation of the cardiac output from the ballistic tracing is based on the results of a comparative study of this method

4. Hamilton, W. F.: Notes on the Development of the Physiology of Cardiac Output, *Federation Proc.* **4**:183-195 (June) 1944.

5. Warren, J. V.; Stead, E. A., Jr., and Brannon, E. S.: The Cardiac Output in Man: A Study of Some of the Errors in the Method of Right Heart Catheterization, *Am. J. Physiol.* **145**:458-464 (Feb.) 1946.

6. Nickerson, J. L.; Warren, J. V., and Brannon, E. S.: The Cardiac Output in Man: Studies with the Low Frequency, Critically Damped Ballistocardiograph and the Method of Right Atrial Catheterization, *J. Clin. Investigation*, to be published. Nickerson and Curtis.^{2b}

and the catheter technic carried out in this laboratory. The derivation of the method of calculating the cardiac output is based on certain theoretic assumptions. Regardless of the validity of these assumptions, empirically the final value obtained from a large series of observations showed satisfactory correlation with almost simultaneous determinations of the cardiac output by the catheter method. The two methods are used to supplement each other, each being useful in particular types of circumstances. The catheter technic, in addition to its value in determining the cardiac output, is useful in measuring the pressures in the chambers of the right side of the heart.

In the following discussion the term cardiac output refers to the minute output of the heart. In all the instances discussed here the stroke volume varied in the same direction as did the minute output. To facilitate comparison of values for cardiac output in persons of different size, the cardiac index is used. This is the output per minute per square meter of body surface.

The left atrial pressure was not recorded. Observations from experiments on animals indicate that the left atrial pressure usually parallels that of the right atrium unless cardiac failure occurs.

EFFECT OF VARYING THE FILLING PRESSURE OF THE VENTRICLES

The work of Starling and his colleagues⁷ has emphasized the effect of venous inflow on the cardiac output. In the heart-lung preparation they observed that the output of the heart was equal to and determined by the amount of blood flowing into the heart and could increase or diminish within wide limits according to the inflow. The greatest output was obtained by increasing the venous inflow until the atrial pressure was moderately elevated. The output of the heart in the usual heart-lung preparation is considerably less than that present in the resting unanesthetized animal.⁸ The maximum output obtained by raising the venous pressure above the normal level is less than the output in the normal dog with a much lower venous pressure.⁹ Starling's experiments demonstrated that there was a relation between the diastolic volume of the ventricles and the energy set free in the following systole. He concluded: "The law of the heart is therefore the same as that of skeletal muscle, namely, that the mechanical energy

7. (a) Patterson, S. W., and Starling, E. H.: On the Mechanical Factors Which Determine the Output of the Ventricles, *J. Physiol.* **48**:357-379 (Sept. 8) 1914. (b) Patterson, S. W.; Piper, H., and Starling, E. H.: The Regulation of the Heart Beat, *ibid.* **48**:465-513 (Oct. 23) 1914.

8. (a) Gollwitzer-Meier, K.; Kramer, K., and Krüger, E.: Der Gaswechsel des suffizienten und insuffizienten Warmblüterherzens, *Arch. f. d. ges. Physiol.* **237**:68-92 (Feb. 18) 1936. (b) Katz, L. N.; Wise, W., and Jochim, K.: The Dynamics of the Isolated Heart-Lung Preparations of the Dog, *Am. J. Physiol.* **143**:463-478 (April) 1945. (c) Patterson and Starling.^{7a}

9. Wiggers, H. C.: Cardiac Output and Total Peripheral Resistance Measurements in Experimental Dogs, *Am. J. Physiol.* **140**:519-534 (Jan.) 1944. Seligman, A. M.; Frank, H. A., and Fine, J.: Traumatic Shock: XII. Hemodynamic Effects of Alterations of Blood Viscosity in Normal Dogs and in Dogs in Shock, *J. Clin. Investigation* **25**:1-21 (Jan.) 1946.

set free on passage from the resting to the contracted state depends on the area of 'chemically active surfaces'; i. e., on the length of the muscle fibers." ^{7a}

While the observation that the output of the heart must depend on its inflow is useful, the experiments of Starling do not elucidate the mechanisms by which the output is increased above the resting level. The maximum output in the preparations studied never reached even the level found in an intact animal of the same size while at rest. It is unusual for the cardiac output in man to fall during the day greatly below the level present under basal conditions. The reserve in the system is in the direction of increasing rather than decreasing the cardiac output. Therefore, one is primarily interested in the means by which the cardiac output is increased above the resting level.

There are several clinical observations which suggest that a change in pressure of the blood in the right atrium is not the primary mechanism by which the normal physiologic variations in cardiac output are produced. The cardiac output of the body at rest is elevated in patients with anemia,¹⁰ thyrotoxicosis,¹¹ arteriovenous fistula¹² and anxiety.^{3c} The right atrial pressure in these conditions is not elevated unless cardiac failure is present. In patients with an arteriovenous fistula in which the lesion is located peripherally, it is possible to determine the right atrial pressure while the cardiac output is lowered by temporarily occluding the fistula with external pressure.¹³ The cardiac output returns to its former level on release of the pressure. At these two greatly different levels of cardiac output, the atrial pressure remains unchanged.¹⁴ Similarly when tourniquets obstructing the arterial inflow into the lower extremities of a normal subject are released, the cardiac output rises without a rise in atrial pressure.¹⁵

10. Sharpey-Schafer, E. P.: Cardiac Output in Severe Anemia, *Clin. Sc.* **5**:125-132 (Aug.) 1944. Brannon, E. S.; Merrill, A. J.; Warren, J. V., and Stead, E. A., Jr.: The Cardiac Output in Patients with Chronic Anemia as Measured by the Technique of Right Atrial Catheterization, *J. Clin. Investigation* **24**:332-336 (May) 1945.

11. Brannon, E. S.; Stead, E. A., Jr., and Warren, J. V.: The Cardiac Output in Thyroid Disease, to be published.

12. Warren, J. V.; Nickerson, J. L., and Elkin, D. C.: The Cardiac Output in Patients with Arteriovenous Fistulas, to be published.

13. Nickerson, J. L.; Elkin, D. C., and Warren, J. V.: The Effect of Temporary Occlusion of Arteriovenous Fistulas on Heart Rate, Stroke Volume, and Cardiac Output, to be published.

14. Warren, J. V.; Cooper, F. W., Jr., and Brannon, E. S.: The Venous and Right Atrial Pressure in Patients with Arteriovenous Fistulas, to be published.

15. Stead, E. A., Jr.; Warren, J. V., and Brannon, E. S.: The Effect of a Large Area of Reactive Hyperemia upon the Cardiac Output and Right Atrial Pressure, to be published.

Administration of certain drugs such as "paredrinol" (2-[2-methylaminopropyl]-phenol)¹⁶ and angiotonin¹⁷ causes a rise in atrial pressure without increasing the cardiac output. Administration of tetraethyl ammonium bromide causes a sharp fall in atrial pressure and a rise in cardiac output.¹⁸

Additional studies have been carried out in this laboratory to observe the effect of variations of right atrial pressure on the output of the heart. The rapid intravenous administration of isotonic solution of sodium chloride and albumin solutions provided a convenient means of temporarily elevating the right atrial pressure in normal subjects. A rise in atrial pressure of as much as 100 mm. of water produced no constant change in cardiac output.¹⁹ Recently, these observations have been confirmed in another laboratory,²⁰ although others believe that they have demonstrated a linear relationship between atrial pressure and cardiac output.²¹

In another group of subjects the effect of lowering the atrial pressure was studied.²² This was carried out either by actually removing 300 to 900 cc. of blood or by pooling a similar amount of blood in the lower extremities by means of tourniquets blocking venous return. In these experiments the atrial pressure was decreased by 30 to 50 mm. of water. The cardiac output at the different levels of venous pressure showed some variation, but there was no consistent relationship to atrial pres-

16. Ranges, H. A., and Bradley, S. E.: Systemic and Renal Circulatory Changes Following the Administration of Adrenin, Ephedrine, and Paredrinol to Normal Men, *J. Clin. Investigation* **22**:687-693 (Sept.) 1943.

17. Bradley, S. E., and Parker, B.: The Hemodynamic Effects of Angiotonin in Normal Man, *J. Clin. Investigation* **20**:715-738 (Nov.) 1941.

18. Stead, E. A., Jr.; Warren, J. V.; Hickam, J., and Cargill, W. H.: Unpublished observations.

19. Stead, E. A., Jr.; Brannon, E. S.; Merrill, A. J., and Warren, J. V.: Concentrated Human Albumin in the Treatment of Shock, *Arch. Int. Med.* **77**: 564-575 (May) 1946. Warren, J. V.; Brannon, E. S.; Weens, H. S., and Stead, E. A., Jr.: The Effect on the Circulation of Normal Subjects of Increasing the Blood Volume and Right Atrial Pressure by Intravenous Infusions, *Am. J. Med.*, to be published.

20. Haynes, B. W., Jr.: The Alterations of Cardiac Output and Plasma Volume in Normal Subjects with the Administration of Concentrated Human Serum Albumin, *Proc. Am. Federation Clin. Research* **2**:74-75, 1945.

21. (a) Barcroft, H.; Edholm, O. G.; McMichael, J., and Sharpey-Schafer, E. P.: Posthaemorrhagic Fainting: Study of Cardiac Output and Forearm Flow, *Lancet* **1**:489-490 (April 15) 1944. (b) Footnote 3 b.

22. Warren, J. V.; Brannon, E. S.; Stead, E. A., Jr., and Merrill, A. J.: The Effect of Venesection and the Pooling of Blood in the Extremities on the Atrial Pressure and Cardiac Output in Normal Subjects with Observations on Acute Circulatory Collapse in Three Instances, *J. Clin. Investigation* **24**:337-344 (May) 1945.

sure. Similar experiments, utilizing the ballistocardiograph, in this laboratory¹⁸ and elsewhere²³ failed to show any significant change in cardiac output after moderate loss of blood. Observations from another laboratory did indicate a decline in cardiac output as the atrial pressure was reduced.^{3b}

If the blood volume is sufficiently decreased by bleeding, the cardiac output will fall and the circulation become inadequate. Clinically, the state of shock will appear. Once the blood volume has been lowered sufficiently to decrease the cardiac output, observations in human beings parallel those reported for the heart-lung preparation. A small change in atrial pressure then causes a great change in output. Indeed, the change in pressure may be so small that it can hardly be measured by the methods used at the present time. The original observations of Starling on the effect of varying the venous inflow at low levels of cardiac output would lead one to expect this.

An analysis of the conditions existing in patients with atrial septal defect is helpful in understanding the relation between atrial pressure and ventricular output. When the patient is at rest, oxygenated blood flows through the septal defect from the left to the right atrium. This has been repeatedly demonstrated by cardiac catheterization.²⁴ It is obvious that if flow from one atrium to the other is to occur a difference in pressure of some degree must exist between the two chambers. Since much of the output of the right ventricle returns to the right side of the heart through the defect in the atrial septum, the output of the right ventricle must exceed that of the left ventricle. It is usually assumed that the large amount of blood presented to the right ventricle is the cause of its inordinately large output.

The flow from left to right atrium demonstrates that the mean pressure in the left atrium is greater than that in the right atrium; therefore, it must follow that the right ventricle is filling to a greater degree than the left ventricle, although the right atrial pressure is less than the left atrial pressure. The normal oxygen saturation of the arterial blood usually present in patients without complicating pulmonary disease or pulmonary arterial disease is proof of the fact that the pressure in the right atrium never exceeds that of the left atrium for a sufficient length of time to create an appreciable shunt from right to left. It is fortunate that the relative atrial pressures in these patients may be determined by the direction of the shunt and

23. Shenkin, H. A.; Cheney, R. H.; Govons, S. R.; Hardy, J. D.; Fletcher, A. G., Jr., and Starr I: On Diagnosis of Hemorrhage in Man: Study of Volunteers Bled Large Amounts *Am J. M. Sc.* **208**:421-436 (Oct.) 1944.

24. Brannon, E. S.; Weens, H. S., and Warren, J. V.: Atrial Septal Defect: Study of Hemodynamics by the Technique of Right Heart Catheterization, *Am. J. M. Sc.* **210**:480-491 (Oct.) 1945.

do not have to be demonstrated by difficult and delicate mechanical measurements.

In summary, it appears that the level of the right atrial or venous pressure, although important in the heart-lung preparation and in patients with a small blood volume, is not an important factor in determining variations in the output of the heart in normal subjects. In the presence of an adequate blood volume, the resultant atrial pressure is sufficient to meet wide variations in cardiac output. The atrial pressure varies considerably in the normal subject, and the body appears to make no effort to maintain it at constant levels. In the wide variety of conditions studied, a normal differential in pressure between atrium and ventricle was adequate to maintain considerable increases in stroke volume. Other means of altering stroke volume, therefore, must be investigated to explain the observed differences in cardiac output.

CHANGES IN ACTIVITY OF VENTRICLES NOT THE RESULT OF CHANGES IN ATRIAL PRESSURE

On theoretic grounds, the stroke volume could be varied equally well by either of two ways without a change in atrial pressure: (1) by increasing the diastolic volume of the ventricles or (2) by more complete emptying of the ventricles. An increase in stroke volume might be caused by either or by a combination of these mechanisms. Means for distinguishing between these two methods of increasing the stroke volume are not available.

Epinephrine.—Epinephrine has long been recognized by physiologists as acting directly on the myocardium, bringing about increased rate and vigor of contraction.²⁵ In moderate dosage in human beings it produces an increase in cardiac output.²⁶ Bradley and Ranges,¹⁶ in studies on two subjects after administration of epinephrine intramuscularly, found that the atrial pressure rose significantly in both. We have studied the effect of small intravenous injections of epinephrine in normal subjects.¹⁸ Increase in the cardiac output occurs early, with little change in atrial pressure. If change occurs at all, there is a slight fall in pressure. This is followed later in most patients by a distinct rise in atrial pressure. Of importance in the present discussion is that the increase in stroke volume occurs without change, or even with a slight fall, in atrial pressure. Records of the pressure in the right ventricle revealed a striking diminution in duration of systole.

Arteriovenous Fistula.—The many vascular injuries of the recent war gave us the opportunity to study the effects of arteriovenous fistulas

25. Best, C. H., and Taylor, N. B.: *The Physiological Basis of Medical Practice*, ed. 4, Baltimore, Williams & Wilkins Company, 1945.

26. Ranges and Bradley.¹⁶ Stead, Warren, Hickam and Cargill.¹⁸

on the circulation in a large number of patients. These observations have been reported in detail elsewhere.²⁷ In the patients with lesions in the extremities the fistula could be rapidly occluded by external pressure. Studies utilizing both the catheter method and the ballistocardiograph have shown that in patients with a large fistula this maneuver is accompanied with a reduction in cardiac output, yet the arterial pressure remains unchanged.¹⁴ On release of the pressure, the output returns to its former level. Most interesting, however, are the studies carried out with the ballistocardiograph, showing the speed of this reaction. Several changes take place within the time of one or, at the most, two heart beats. The heart rate slows, the stroke volume decreases and the arterial pressure increases. In many instances the change in arterial pressure is only slight. On release of the pressure, these functions quickly return to their original level. The slowing of the heart is prevented if the patient is given atropine before the fistula is compressed. This gives evidence that the change in heart rate is a reflex response mediated by the vagus nerve. The change in stroke volume occurs despite the use of atropine.

Reactive Hyperemia.—Circulatory phenomena similar to those observed in patients with arteriovenous fistula may be demonstrated in normal subjects.¹⁵ Blood pressure cuffs placed around the legs as high as possible and inflated to 200 mm. of mercury cause only minimal circulatory changes. If the cuffs are left on for fifteen to twenty minutes and then released, a period of so-called reactive hyperemia occurs in the legs. The flow of blood through the area becomes large, so that in certain respects a temporary arteriovenous fistula is formed. This reaction gradually subsides during the next few minutes. The release is accompanied with circulatory changes similar to those observed on release of a compressed arteriovenous fistula. The pulse rate increases, the stroke volume increases, the arterial pressure may fall slightly, but the atrial pressure shows little change. If any is noted, there is a slight fall. Thus, again there is a rapid increase in cardiac output without alteration in filling pressure occurring with such rapidity as to preclude a humoral mechanism.

To be sure that the rise in cardiac output is not due to a large mass of blood returning to the heart without a detectable increase in atrial pressure, the experiment was modified. In addition to the arterial tourniquets, another set was applied at a pressure of 30 mm. of mercury. Care was taken that the legs were emptied of blood by elevating them when the arterial tourniquets were applied. On release of the tourniquets applied at a high pressure, any return flow of blood to the heart was temporarily stopped by the tourniquets applied at a low pressure. Nevertheless, the change in cardiac rate and output occurred as before.

27. Warren, Nickerson and Elkin¹²; footnote 13.

These observations on the effect of epinephrine, arteriovenous fistulas, and reactive hyperemia all demonstrate changes in cardiac output not associated with significant changes in atrial pressure.

The increase in stroke volume with the use of epinephrine seems most likely to be on a humoral basis, the epinephrine acting directly on the ventricle muscle. The increase in cardiac output produced by the opening of an arteriovenous fistula or by reactive hyperemia occurs so rapidly that a humoral mechanism does not appear possible. The increase in cardiac output appears to be related to the opening of an area of low peripheral resistance in the arterial tree.

Assuming that variations in cardiac output may occur in the absence of a change in atrial pressure and that alterations in the stroke volume of the ventricle may be produced by lowering of peripheral resistance, let us examine some of the physiologic and pathologic conditions associated with a modified cardiac output. Anemia and anoxia are two common ones. In both, the amount of blood normally sufficient to supply the needs of the body tissues no longer is able to do so. More blood is needed, and if the cardiovascular system is competent, more is delivered. Studies on patients with severe chronic anemia have revealed that the cardiac output is increased, the peripheral resistance is strikingly diminished and the atrial pressure is normal.¹⁰ It appears possible that the increased cardiac output results from the decreased peripheral resistance just as it does in our subjects with reactive hyperemia. Although far from proved, it is an attractive hypothesis that throughout the body a more or less chronic state of reactive hyperemia exists in order to supply an adequate amount of blood to the tissue. Only by remaining dilated can the peripheral vessels receive, and in turn, deliver to the tissues, an adequate amount of oxygen. A similar mechanism would appear to be operative in anoxia.

Thyrotoxicosis is accompanied with an increase in output of the heart, and, conversely, myxedema is accompanied with a diminished output.²⁸ Studies by the catheter method have shown that these changes occur in the absence of altered atrial pressure and with relatively normal venous oxygen tension. In other words, the arteriovenous oxygen difference remains relatively normal, the alterations in output varying with the consumption of oxygen. Factors similar to those involved in fever may be operative here, except that the altered requirements of the tissues are the result of a humoral rather than a thermal stimulus.

Anxiety and Exercise.—Psychic factors, as already mentioned, may alter the output of the heart.^{8c} Independent of an increase in consumption of oxygen (basal metabolic rate) and pulse rate, the output may be doubled in a person tense and anxious. The atrial pressure is normal.

28. Brannon, Stead and Warren.¹¹ Grollman.^{1b}

The peripheral resistance is greatly lowered, but usually not to a sufficient degree to compensate for the increase in cardiac output. The systolic, diastolic and mean arterial pressures increase, therefore.

Exercise is a potent cause of increased output of the heart.^{1b} Here many factors may be involved, such as psychic stimuli, increased metabolic requirements by the tissues and the increased requirements for dissipation of heat. The effect of the increased respiratory movements and increased muscular contraction is not clear. Because of the difficulty in studying the subject during the violent motions of exercise, little is known. The increase in cardiac output by light exercise may occur without a measurable change in right atrial pressure. The peripheral resistance does not usually fall sufficiently to prevent a rise in the arterial pressure from the increase in cardiac output.¹⁸

The reason for the large output of the right ventricle in patients with an atrial septal defect has not been determined. Since the right ventricle is receiving more blood than the left ventricle in the presence of a lower filling pressure, it is clear that the cause of the increased output of the right ventricle must result from some abnormality in the control of the right ventricular output not dependent on atrial pressure. The increased output of the right ventricle has been found to continue in the presence of striking pulmonary hypertension.²⁴ This would suggest that the abnormal circulation was not due merely to diminished peripheral resistance in the pulmonary circuit.

POSSIBLE MECHANISMS TO ACCOUNT FOR INCREASE IN CARDIAC OUTPUT
PRODUCED BY DECREASE IN PERIPHERAL RESISTANCE

Mechanical Effect From Lowering Peripheral Resistance.—The fall in arterial pressure might increase the stroke volume by mechanically permitting the ventricle to empty more completely. This would assume that residual blood remaining in the ventricles is sufficient to make up the observed increase in systolic output. Although it is not certain whether the normal ventricles empty completely, it appears unlikely that there is a large quantity of residual blood.²⁹ Westermarck³⁰ has studied the circulation roentgenologically in rabbits by means of moving pictures made during the passage of contrast mediums through the vascular system. Systolic contraction was found to empty the ventricles almost completely while at all times the atria contained considerable blood. In certain pathologic states, however, complete emptying of the ventricles undoubtedly does not occur. Large dilated hearts contain

29. Nylin, G.: On the Amount of, and Changes in, the Residual Blood of the Heart, *Am. Heart J.* **25**:598-608 (May) 1943.

30. Westermarck, N.: On Circulation Through Heart, Big Vessels, and Pulmonary Circulation Simultaneously Recorded by Cinematography, *Acta radiol.* **23**:473-510 (Oct. 3) 1942.

considerable residual blood.²⁹ In patients with such hearts the increased stroke volume associated with digitalis therapy is accompanied with a decrease in diastolic volume of the heart.³¹ In these circumstances an increased output appears to result from more complete ventricular emptying.

Observations on patients with reflex fainting and postural hypotension demonstrate that a fall in peripheral resistance does not mechanically result in a rise in cardiac output if the autonomic nervous system is not functioning normally. The increases in cardiac output produced by anxiety and by exercise occur with a rise rather than a fall in mean arterial pressure.

Reflex Stimulation of Ventricles.—The immediate change in cardiac output and rate with compression and opening of an arteriovenous fistula is too rapid to be caused by a humoral mechanism. The decided shortening of systole and the rise in right ventricular pressure which are produced by the administration of epinephrine do not occur when the cardiac output is increased by opening an arteriovenous fistula. Both stroke volume and rate change within the space of one beat, and the change is maximal within one or two beats. The change in rate is a vagal reflex inhibited by the administration of atropine. The change in stroke volume is not altered by the use of atropine. It occurs in patients with fistulas of the lower extremity after high spinal anesthesia.

The release of arterial tourniquets likewise causes an immediate rise in cardiac rate and output. The response differs from that obtained on release of an arteriovenous fistula in that the maximal changes in cardiac rate and output do not occur immediately.

It is interesting to speculate on the possibility that the output of the heart in the presence of an adequate volume of blood may be controlled primarily by reflex stimuli acting directly on the ventricles. Afferent stimuli might arise from a lowering of the arterial pressure, from moving muscles, from the emotional content of thought and from many other sources. If such reflexes occur, they are not paralyzed by atropine and have a very short latent period.

Clinical Observations Which Support the Concept That the Cardiac Output is Under Reflex Control.—If reflexes acting on the ventricles were important in the control of the cardiac output, one would expect to find instances in which there was evidence of confusion in the reflexes. Physicians are familiar with the respiratory incoordination in patients with Cheyne-Stokes breathing and with neurocirculatory asthenia. Similar instances of incoordination are found in the circulation.

31. Cohn, A. E., and Steele, J. M.: Studies on the Effect of the Action of Digitalis on the Output of Blood from the Heart: I. The Effect on the Output of the Dog's Heart-Lung Preparations, *J. Clin. Investigation* **11**:871-895 (Sept.) 1932.

Starr has emphasized this incoordination in patients with neurocirculatory asthenia. In the common faint there is evidence of diffuse overactivity of the autonomic nervous system, with widespread signs of gross incoordination of the reflexes.³² Despite the presence of the pronounced decrease in peripheral resistance, the cardiac output in these patients does not increase as the arterial pressure falls. If it did, the fall in arterial pressure would not be nearly so profound. It would appear possible that the heart is inappropriately, but reflexly, inhibited from responding normally in this situation.

Persons with postural hypotension likewise display evidence suggestive of abnormal function of the nervous mechanism controlling the heart. Widespread involvement of the autonomic nervous system had been demonstrated in these patients.³³ Frequently the heart rate is relatively fixed and does not increase when the person is standing or after administration of atropine. In these patients the postural fall in arterial pressure is not compensated for by a rise in cardiac output.

CONCLUSIONS

The output of the heart in the presence of an adequate volume of blood is varied by changes in ventricular relaxation and contraction which are independent of fairly wide variations in atrial pressure. The ventricles play an active rather than a passive role in determining the cardiac output. Lowering of the arterial pressure by opening an auriculo-ventricular fistula or by opening large areas of reactive hyperemia causes an abrupt rise in cardiac output which occurs too rapidly for a humoral mechanism. Anxiety and exercise cause a rise in cardiac output in the presence of an increase in arterial pressure. It is suggested that reflex stimulation of ventricular activity accounts for the changes in cardiac output during daily activity and that the afferent stimuli may arise in part from a lowering of the arterial pressure, the movement of the limbs during exercise and the emotional content of thought. Appreciation of the fact that changes in atrial pressure are not the primary factors in increasing the cardiac output during daily work opens a wide field for investigation.

32. Warren, Brannon, Stead and Merrill.²² Barcroft, Edholm, McMichael and Sharpey-Schafer.^{21a}

33. Stead, E. A., Jr., and Ebert, R. V.: Postural Hypotension: A Disease of the Sympathetic Nervous System, *Arch. Int. Med.* **67**:546-562 (March) 1941. Ellis, L. B., and Haynes, F. W.: Postural Hypotension with Particular Reference to Its Occurrence in Diseases of the Central Nervous System, *ibid.* **58**:773-798 (Nov.) 1936.

SARCOIDOSIS IN SIBLINGS

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SARCOIDOSIS, or benign lymphogranulomatosis (Besnier-Boeck-Schaumann disease), is now recognized as a relatively common clinical and pathologic entity. In extensive reviews of the subject¹ by various authors the symptoms, clinical course and pathologic findings have been described in detail, so that further comment in this respect is unnecessary.

In spite of the wealth of reports of cases in the literature, only four references to sarcoid in siblings have been found, all from continental Europe. Dressler described Boeck's disease of the lungs in a brother and sister² and, in a later paper, in 2 brothers.³ In all 4 of his cases, the diagnoses were based on the benign course of the disease, roentgenologic findings in the lungs, negative reactions to tuberculin tests (except in 1 case), negative reactions in guinea pigs on inoculation, and inability to find tubercle bacilli on repeated examinations of sputum. Boggild⁴ reported probable Boeck's sarcoid of the fingers in sisters 2 and 5 years old. His diagnoses were based solely on the finding of small cystic areas in the bones by roentgenologic examination. Sellei and Berger⁵ described a family in which the condition in 5 of 7 siblings

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1. Goeckerman, W. H.: Sarcoids and Related Lesions, *Arch. Dermat. & Syph.* **18**:237 (Aug.) 1928. Thomas, C. C.: Sarcoidosis, Including Fifteen Cases, Twelve in Negroes, *ibid.* **47**:58 (Jan.) 1943. Longcope, W. T.: Besnier-Boeck-Schaumann Disease: Frank Billings Lecture, *J. A. M. A.* **117**:1321 (Oct. 18) 1941. Longcope, W. T., and Pierson, J. W.: Boeck's Sarcoid (Sarcoidosis), *Bull. Johns Hopkins Hosp.* **60**:223 (April) 1937. Reisner, D.: Boeck's Sarcoid and Systemic Sarcoidosis (Besnier-Boeck-Schaumann Disease): Thirty-Five Cases, *Am. Rev. Tuberc.* **49**:289 (April); 437 (May) 1944.

2. Dressler, M.: Boeck's Disease of Lungs in Siblings: Two Cases, *Schweiz. med. Wchnschr.* **68**:417 (April 23) 1938.

3. Dressler, M.: Familial Occurrence of Besnier-Boeck's Disease in Lung, *Schweiz. med. Wchnschr.* **69**:269 (March 25) 1939.

4. Boggild, D.: Probable Boeck's Sarcoid of Fingers in Sisters Two and Five Years Old: Two Cases, *Nord. med. (Hospitalstid.)* **21**:416 (March 3) 1944.

5. Sellei, J., and Berger, M.: Sarcoid Tumors in a Family: Sarcoid (Joseph) and Lupoid-Allergic Reaction, *Arch. f. Dermat. u. Syph.* **150**:47, 1926.

was diagnosed as sarcoid by the clinical courses of the patients and typical histologic pictures of tissue on biopsy. To these reports we add the records of examples of familial sarcoid.

FIRST FAMILY

CASE 1.—W. H. B., a 25 year old Negro, was first seen in the Johns Hopkins Hospital on June 13, 1946, with the chief complaint of "trouble in his chest, back and eyes." For four or five months he had had pain in the region of the kidney, which was worse on bending or stooping. There was also pain along the lower wall of the right side of the chest under the ribs, almost constantly present. For "some time" there had been redness and pain in both eyes and swelling in the parotid region (the first symptom, preceding any other by several months). He had lost 20 pounds (9 Kg.). By the time of examination the parotitis had almost completely subsided. There was some questionable dyspnea, not related to exertion. In September 1945 he noticed edema of the ankles, which gradually subsided, leaving the legs scaly. The only significant fact in the family history was that a brother had had "some sort of eye trouble." There was no history of tuberculosis. The past history and a review of the systems were essentially noncontributory.

Physical Examination.—The temperature was 100 F., the pulse rate 116 and the respiratory rate 24. The height was 66½ inches (169 cm.) and the weight 132¼ pounds (60 Kg.). The blood pressure was 110 systolic and 80 diastolic. The patient was a young Negro who had obviously lost weight and who appeared ill and somewhat pale. There was no respiratory distress. An eruption was seen on both forearms just above the wrists in the form of an annular arrangement of subcutaneous nodules, the skin over which was slightly hyperpigmented. Similar, less conspicuous nodules were present on the anterior aspect of both thighs and the left side of the scrotum. The skin over the lower part of the legs was thickened and scaly, and the hair in this region seemed brittle. There was slight tenderness over the long muscles of the back. Slight generalized glandular enlargement was noted, particularly of the posterior cervical nodes. The parotid glands were definitely enlarged. There was some injection of the conjunctivas, and the upper lids appeared swollen. The pupils were irregular in outline, due to the presence of synechias, and they reacted sluggishly to light. Medial opacities prevented accurate funduscopic examination. Hearing was poor in the right ear. The lungs were entirely clear except for questionable bronchovesicular breathing over the right infraclavicular area. The examination of the heart was noncontributory. Examination of the abdomen was made difficult by voluntary muscular tension. There was definite tenderness in the epigastrium, but no masses were felt. The remainder of the physical examination and a urinalysis showed no abnormalities.

Diagnostic possibilities considered at the time of the examination were sarcoid, tuberculosis, syphilis, brucellosis and tularemia.

Laboratory Reports.—The nonprotein nitrogen content was 38 mg. per hundred cubic centimeters, the total protein content was 6.81 Gm. and the albumin-globulin ratio was 4.50:2.31. The white blood cell count was 6,600 and the hematocrit reading 44.2. The corrected sedimentation rate was 1.0 mm. A serologic test of the blood for syphilis gave negative results. Agglutination tests for tularemia, gonorrhea and brucellosis gave negative results; reactions to typhoid tests were positive with O antigen in a dilution of 1:80 and doubtful with H antigen in a dilution of 1:40. Tuberculin tests with 0.001 to 0.1 mg. of old

tuberculin elicited negative reactions; a test was done with 1.0 mg., but the reaction was not read.

A roentgenologic examination of the chest showed no abnormalities of the ribs, but dense infiltrations in the region of the roots of both lungs were described as being compatible with a diagnosis of sarcoid. No evidence of sarcoid was seen in the bones of the hands, and examination of the thoracic and lumbar regions of the spine showed nothing abnormal.

One of the papules on a forearm was removed for biopsy. The histologic picture was interpreted by Dr. Lloyd Ketron as typical of sarcoid on the basis of nests of epithelioid cells in the corium, separated by connective tissue septums, the presence of giant cells and the absence of caseation.

CASE 2.—T. B., the brother of W. H. B., was a 29 year old Negro who was first seen in the Johns Hopkins Hospital on March 20, 1944, with the complaint of pain in the back. The family history and past history were noncontributory. The review of the systems was essentially noncontributory.

In August 1943 the patient had first noticed a dull, aching, nonradiating pain, with no associated symptoms, in both sides of the lower part of the back, associated with movement. In December 1943 the pain had become more constant and occurred even at rest, and swelling of the ankles and periorbital region had begun.

During January 1944, the patient noticed what he described as "visual difficulty" in the right eye. This persisted to the time of examination, along with a burning sensation in both eyes. Loud noises caused distress in the right ear. Early in February 1944 he noticed swelling of the neck and symmetric preauricular knots. In March 1944 the patient noticed aching in the left forearm, radiating to the fifth finger, generalized itching and sore throat associated with a non-productive cough.

Physical Examination.—The temperature was 97.6 F., the pulse rate 84 and the respiratory rate 20. The weight was 138¾ pounds (63 Kg.) and the height 70½ inches (179 cm.). The blood pressure was 112 systolic and 85 diastolic. The patient was a frail young Negro. The skin was of normal texture except over the lower half of the legs, where it was scaly and roughened. The lungs were entirely clear. The examination of the heart revealed nothing unusual except for a split second sound over the precordium. There were no abnormal abdominal findings.

Both testes were unusually tender, but they were not otherwise abnormal. The finger nails were cyanotic, and the lower parts of the legs and the feet were edematous. Neurologic examination revealed paralysis of the right seventh cranial nerve of the lower motor neuron type. The remainder of the physical examination revealed nothing significant. Urinalysis revealed nothing unusual except for 2 or 3 leukocytes and 1 or 2 granular casts per high power field.

The diagnostic impression at this time was parotitis (?), unaccountable edema of the ankles and nephrosis (?).

Laboratory Reports.—The hematocrit reading was 45; the white blood cell count was 4,950; the corrected sedimentation rate was 4.0 mm. in one hour, and the icterus index was 7.5. The serologic test for syphilis gave negative results.

Roentgenologic examination of the chest showed a normal heart and aorta. There was dense clouding in each hilus and infiltration extending therefrom to involve each lung, slightly less pronounced at the bases and apexes. There was probably some enlargement of the lymph nodes at each hilus, but these were not discrete. The appearance was interpreted as being compatible with a diagnosis

of sarcoid. The roentgenogram of the hands was normal except for slight thickening of the soft tissues in the region of the proximal interphalangeal joints.

On March 28, 1944 the patient returned to the hospital with a complaint of soreness in the right eye. There was conjunctival injection and photophobia, and uveoparotid fever was considered the best possibility. He was admitted to the hospital for study. Examination on admission showed essentially the same findings as on the previous examination except for the additional presence of a dilated, fixed pupil of the right eye, blurring of the disk of the left eye, scattered crackling rales in the lower field of the left lung and indurated, enlarged and tender epididymides. The diagnostic impression then was sarcoidosis with uveitis, parotitis, Bell's palsy of the right side and bilateral epididymitis. The corrected sedimentation rate was now 16 mm. in one hour. The reaction to a tuberculin test with 0.02 mg. of purified protein derivative was negative. A biopsy of a femoral node showed only scarring and deposits of hemosiderin. The patient's three week course in the hospital was afebrile except for occasional elevations in temperature to 100 F.

After his discharge the patient was not seen again until July 27, 1944, when he returned to the hospital because of weakness of the left side of the face. The roentgenogram of his chest now showed, in addition to the previous findings, slight infiltration in the lower lobe of each lung. On Aug. 7, 1944, an ophthalmologic consultant stated that he had found bilateral granulomatous iritis which was probably due to sarcoid. On Jan. 4, 1945, roentgenologic examination of the chest showed no change. On July 20, 1945, he returned to the hospital with exacerbation of the uveitis of the left eye. Reaction to a tuberculin test at this time was negative with 0.1 mg. of old tuberculin.

SECOND FAMILY

CASE 3.—I. S., a 31 year old Negro, was first seen at Johns Hopkins Hospital on Nov. 13, 1937, having been referred for diagnosis. A complete report of this visit is not obtainable, but three nodes in the right inguinal area were excised and a biopsy specimen was taken from a finger after a clinical impression of sarcoid had been gained. The pathologic report stated that there were "hard and caseous tubercles and giant cells in the subcutaneous tissue of the finger. The clinical picture of sarcoid was present. No tubercle bacilli were found."

In September 1938 the patient was again seen, and a note was made that there were typical sarcoid lesions of the skin, especially on the arms and legs. At this examination the question of pulmonary tuberculosis was raised, as tubercle bacilli were said on one occasion to have been found in the sputum by a substitute technician. This, however, was not confirmed by subsequent examinations of the sputum.

Because of ulceration of some of the cutaneous lesions, frequency of symptoms, nocturia and hematuria, the patient was admitted to the medical service on Nov. 24, 1940.

At this time the information was obtained that he had been "sickly" since childhood, with frequent stomach aches, poor appetite and general lassitude. He had had no known contact with tuberculosis. At 18 years of age he had pneumonia with empyema, necessitating open drainage.

In 1934 he noticed swelling of the cervical lymph nodes, followed by swelling of both sides of his face. His tonsils were removed, and the swelling became more severe. At the same time he had considerable visual difficulty, with photophobia, inflammation and inability to recognize distant objects. Later, there was a definite droop of the left eyelid and his mouth became twisted to the right. The

parotitis and facial palsy gradually subsided and were succeeded by subcutaneous "lumps" in the skin, varying from pinhead sized to pea sized and nontender but itching. The swelling of the neck subsided early in 1936, but the cutaneous lesions persisted.

In March 1937, at another hospital, a roentgenogram of the fingers showed thickened soft tissues of the index finger of the left hand at the proximal interphalangeal joint. Roentgenologic examination of the chest showed an area of increased density in the lower lobe of the right lung and a large area of decreased density in the upper lobe of that lung, with possible cavitation, diffuse pleural thickening on the right, infiltration of the upper lobes of both lungs, suggestive of tuberculosis, and decided increase in the shadows of the roots. Smear cultures of the sputum failed to reveal tubercle bacilli. The corrected sedimentation rate was 40 mm. in one hour.

Physical Examination (Nov. 24, 1940).—The temperature was 99.8 F., the pulse rate 108 and the respiratory rate 24. The weight was 138 pounds (62.5 Kg.) and the height 68 inches (173 cm.). The blood pressure was 152 systolic and 110 diastolic. The patient was a well developed young Negro who appeared ill. There was a scaly dermatitis of the scalp and extremities, consisting of dry crusted nodules varying from 2 mm. to 2 cm. in diameter. Small nodules were seen in the eyelids. Motion of the right side of the chest was limited, and there was a curvature of the spine to the left. The right side of the chest was dull to percussion, and scattered rales were heard over both pulmonary fields, especially after coughing. The spleen was easily felt, and there were epitrochlear lymphadenopathy involving the right arm and a fusiform swelling of some of the fingers, especially the left index finger. The remainder of the physical examination was essentially noncontributory.

Laboratory Reports.—The blood picture was normal except that 7 per cent of the cells were eosinophils. A serologic test of the blood for syphilis gave negative results. Repeated smears and cultures of the sputum failed to reveal tubercle bacilli. The nonprotein nitrogen content of the blood was 44 mg. and the total protein content 7.6 Gm. per hundred cubic centimeters. The albumin-globulin ratio was 44:56. The basal metabolic rate was +20 per cent. The uric acid content of the blood was 5.7 mg. per hundred cubic centimeters and the cholesterol content 160 mg. In a phenolsulfonophthalein test 78 per cent of the dye was excreted in two hours. A series of gastrointestinal roentgenograms revealed a duodenal ulcer. Dr. Murray Fisher, who had been interested in the patient since 1937, was of the opinion that he had had sarcoid and that active tuberculosis had developed later. On December 23 the patient became suddenly worse, with gradually deepening coma, and he died in renal failure and alkalosis on December 27.

The pathologic diagnosis was as follows: sarcoid, with lesions in the skin, lymph nodes, lungs, pleura, liver, spleen, kidneys, testes and epididymides; scars and infiltration of mononuclear cells in the heart (healed sarcoid?); old healed tuberculosis (?) with formation of cavities in the upper lobes of both lungs; tuberculosis of the axillary lymph nodes on the right, with a sinus tract; old resection of the ribs on the right side; fibrous pleural and pericardial adhesions; history of terminal alkalosis; deposition of calcium in the renal tubules, and bilateral renal calculi.

The cavities in the lungs were surrounded by fibrous walls. No caseation was seen. The fibrous walls contained sarcoid tubercles and were surrounded with sarcoid tissue. The axillary lymph node showed typical tuberculosis in which caseation was evident and tubercle bacilli were stained. Tubercle bacilli were

found in none of the sarcoid lesions. It was the opinion of the pathologist that the cavities were not the result of sarcoid but were probably tuberculous in origin.

CASE 4.—C. S., a brother of I. S., was a 21 year old Negro, first seen in the Johns Hopkins Hospital on Dec. 21, 1938, complaining of a "sore knee joint." Ten months prior to his first visit he had lost his appetite and had noticed some shortness of breath and tachycardia. Loss of weight, which began at the same time, continued progressively up to the time of his admission to the hospital. His sputum had been examined elsewhere in April 1938, and no tubercle bacilli had been found. On November 1 his tonsils became sore and the glands under the angles of the jaw became swollen. The attacks of tonsillitis continued intermittently. A few days prior to his first visit the right knee became sore and swollen. There was no history of trauma. No other joints were involved.

Physical Examination.—The temperature was 99.8 F., the pulse rate 88 and the respiratory rate 20. The weight was 145½ pounds (66 Kg.) and the height 69½ inches (177 cm.). The blood pressure was 110 systolic and 75 diastolic. The patient was a well developed young Negro, in no obvious distress. Both tonsils were found to be mildly inflamed. The right knee was swollen, hard and tender, but there was no crepitus. The remainder of the physical examination was essentially noncontributory. Other than moderate albuminuria, urinalysis revealed nothing abnormal.

The first impression was that the patient had acute rheumatic fever, and salicylate therapy was given, without improvement. A roentgenogram of the chest showed diffuse infiltration throughout both pulmonary fields, extending from the roots of the lungs. There was definite enlargement of the hilar nodes, and the picture was interpreted by the radiologist as nontuberculous but compatible with a diagnosis of sarcoid, Hodgkin's disease or leukemia. A roentgenogram of the right knee showed fluid and pathologic changes interpreted as being due to acute infection. It was then recalled that his brother (case 3) had sarcoid, and he was admitted to the hospital for study on Dec. 28, 1938.

The only additional finding of significance at this time was that of generalized lymphadenopathy. A node in the right supraclavicular area was excised. The histopathologic picture was that of sarcoid, the lymph nodes being replaced by large tubercles, a few of which contained giant cells. The tubercles were poorly defined but were separated in some areas by narrow rows of plasma cells. In places there were small collections of lymphocytes and numerous epithelioid cells. Acid-fast stains revealed nothing unusual. Biopsy of the synovial tissue of the knee joint showed only chronic inflammation.

Laboratory Reports.—The total protein content was 6.64 Gm. per hundred cubic centimeters; the albumin-globulin ratio was 42:58. Reaction to a tuberculin test with 0.1 mg. of old tuberculin was negative. The electrocardiogram was normal. Agglutination tests for brucellosis and tularemia gave negative results.

On Jan. 24, 1939 an ophthalmologist found evidence of old uveitis, although the patient denied symptoms. He was not seen again until Jan. 23, 1942, when he returned with a complaint of hoarseness of five months' duration. Tubercle bacilli were found on examination of the sputum, and a roentgenogram of the chest showed extensive tuberculous infiltration, with cavities in both apexes. Since that time he has had two admissions to a sanatorium for patients with tuberculosis.

A notation in a record of the patient's history on Oct. 19, 1942 stated that "a sister, F. H., who also had sarcoid, died on Oct. 18, 1942."

CASE 5.—H. S., the brother of I. S. and C. S., was a 22 year old Negro who came to the Johns Hopkins Hospital on Jan. 28, 1939, by request, because of a history of sarcoidosis in two of his brothers. His past history was noncon-

HEPATITIS WITHOUT JAUNDICE IN INFECTIOUS MONONUCLEOSIS

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JAUNDICE was first recognized as a complication of infectious mononucleosis by Mackey and Wakefield in 1926.¹ A single case in which a patient with this disease exhibited jaundice had been noted previously by Downey and McKinlay.² The incidence of jaundice in different reported series of cases of infectious mononucleosis has varied from 1.3 to 12.8 per cent.³ At first, it was postulated that jaundice was due to blocking of the common duct by enlarged lymph glands.⁴ Later evidence acquired by tests of hepatic function⁵ and by biopsies of material obtained with the punch⁶ indicates that jaundice is secondary to parenchymatous changes in the liver. From a single biopsy of the liver, Kilham and Steigman^{6a} described a well defined focal acute hepatitis. They said: "the maximum change is seen in the portal tracts of the lobules where there is loss of liver cells and a well developed histiocytic reaction with some early proliferation of bile ducts."

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1. Mackey, R. D., and Wakefield, E. G.: The Occurrence of Abnormal Leukocytes in the Blood of a Patient with Jaundice (Infectious Mononucleosis-Glandular Fever), *Ann. Clin. Med.* **4**:727 (March) 1926.

2. Downey, H., and McKinlay, C. A.: Acute Lymphadenosis Compared with Acute Lymphatic Leukemia, *Arch. Int. Med.* **32**:82 (July) 1923.

3. (a) Immerman, S. L.: An Epidemic of Infectious Mononucleosis, *M. Rec.* **157**:480 (Aug.) 1944. (b) Spring, M.: Jaundice in Infectious Mononucleosis, *Bull. U. S. Army M. Dept.*, October 1944, no. 81, p. 102.

4. Bernreiter, M.: Infectious Mononucleosis: Treatment with Sulfanilamide, *J. Kansas M. Soc.* **39**:513 (Dec.) 1938. Mackey and Wakefield.¹

5. Mason, V. R.: Jaundice in Acute Infectious Mononucleosis (Glandular Fever), *California & West. Med.* **29**:187 (Sept.) 1928. Morris, M. H.; Robbins, A., and Richter, E.: Acute Infectious Mononucleosis with Hepatitis: Presentation of Two Cases, *New York State J. Med.* **442**:1579 (July 15) 1944. Spring.^{3b}

6. (a) Kilham, L., and Steigman, A.: Infectious Mononucleosis, *Lancet* **2**:452 (Oct. 17) 1942. (b) Bang, J., and Wanscher, O.: Leverenshistopatologi ved mononucleosis infectiosa kompliceret med icterus, undersøgt ved aspirationsbiopsi, *Nord. med. (Hospitalstid.)* **24**:2175 (Dec. 8) 1944.

Laboratory Reports.—There were no abnormal contents in the urine. The reaction to a tuberculin test was positive in forty-eight hours with 1.0 mg. of old tuberculin. A roentgenogram of the chest showed linear fibrosis extending from the roots of both lungs into the perihilar regions.

COMMENT

In the first family there were 3 siblings, only 2 of whom were examined and found to have sarcoidosis. Nothing is known of the third member. There is a remarkable similarity in the symptoms and clinical course of the disease in these 2 brothers. In only 1 (case 1) did the report of the biopsy confirm the clinical impression, but there is little doubt about the diagnosis in case 2. Typical cutaneous lesions were present only in the first patient.

The second family was studied in detail so far as possible (several of the siblings lived in another state and were not available for examination). There were 10 siblings, 5 of whom were examined in the Johns Hopkins Hospital. Of the 5 who were examined, 3 (cases 3, 4 and 5) were proved to have sarcoidosis by roentgenologic examination, negative reactions to tuberculin tests at first examination and biopsy. Although the diagnosis was not proved in case 6, it is highly probable that the patient had sarcoid in view of the iritis, parotitis, only slightly positive reaction to the tuberculin test with 1.0 mg. of old tuberculin and subsequent appearances in the roentgenograms. One other patient who was examined at the Johns Hopkins Hospital is not reported on in detail because of lack of sufficient evidence for a definite diagnosis. However, sarcoid is suspected in this patient also.

There is a notation in the record of the history of the patient in case 4 which states that a sixth sibling had died after a diagnosis of sarcoid had been made elsewhere. No confirmation of this statement is available.

In only 1 member of this family (case 3) were definite cutaneous lesions described by the examining physicians.

Active tuberculosis ultimately developed in the patients in cases 3 and 4, but in each instance three years had elapsed since the original diagnosis of sarcoid had been established by repeated negative results of examinations of sputum, negative reactions to tuberculin tests, uveo-parotitis and biopsy.

SUMMARY

Sarcoidosis occurred in siblings of two unrelated families. In one family at least 2 of the 3 siblings were affected, and in the other a diagnosis was established for 3 siblings and was probable or possible for at least 3 others of a total of 10 siblings. Cutaneous lesions were found in only 2 of the patients discussed. Active tuberculosis ultimately developed in 2 patients.

Dr. Murray Fisher of the Department of Medicine, Johns Hopkins Hospital, allowed us to use the material which he had accumulated regarding family 2.

Heterophile antibody tests were performed by the original technic of Davidsohn¹⁰ and recorded according to actual serum dilution.⁷ Agglutination in a dilution of 1 to 160 or over was considered as a positive reaction. Tests of hepatic function performed routinely were the icterus index test, the cephalin-cholesterol flocculation test¹¹ and the sulfobromophthalein excretion test. Normal values for the icterus index range from 4 to 7 units.¹² For the cephalin-cholesterol flocculation test, values of 2 plus or over in forty-eight hours or less were considered abnormal.¹³ In the performance of the sulfobromophthalein test, 5 mg. of the dye per kilogram of body weight was injected and blood was drawn either in forty-five minutes or in thirty and sixty minutes. Retention of dye up to 10 per cent in thirty minutes¹⁴ and complete excretion in forty-five minutes and sixty minutes¹⁵ were considered normal. Determinations of serum albumin and globulin contents were made in 9 cases.

RESULTS

Some degree of hepatic dysfunction as shown by the cephalin-cholesterol flocculation and/or the sulfobromophthalein excretion test was present in all 19 cases of infectious mononucleosis (table). The icterus index was normal in 13 cases, and in 5 it ranged from 8 to 10 units. These values may represent slight hyperbilirubinemia, but no clinical jaundice was present. The reaction to the cephalin-cholesterol flocculation test was positive in 15 of 18 cases in which the test was performed. Of the 3 cases in which the reaction was negative, in 2 (cases 1 and 4) the disease was in a late stage and in 1 (case 15) there was an extremely mild form of the disease. Hepatic damage in these 3 patients was indicated by the retention of sulfobromophthalein. In most cases the reaction to the cephalin-cholesterol flocculation test was still positive after the excretion of sulfobromophthalein had returned to normal. The sulfobromophthalein test showed an abnormal retention in 15 of the 19 cases. The maximum retention was 36 per cent (case 8) in forty-five minutes. All the 4 patients having no retention of dye had a positive reaction to the cephalin-cholesterol flocculation test. An abnormal albumin-globulin ratio was present in 2 (cases 1 and 16) of 9 cases.

10. Davidsohn, I.: Heterophile Antibodies in Serum Sickness, *J. Immunol.* **16**: 259 (March) 1929.

11. The cephalin-cholesterol mixture prepared by Wilson Laboratories, Chicago, was used.

12. Wintrobe, M. M.: *Clinical Hematology*, Philadelphia, Lea & Febiger, 1942, p. 78; reprinted, 1944.

13. Hanger, F. M.: Serological Differentiation of Obstructive from Hepatogenous Jaundice by Flocculation of Cephalin-Cholesterol Compounds, *J. Clin. Investigation* **18**:261 (May) 1939.

14. Israel, H. L., and Reinhold, J. G.: Detection of Cirrhosis and Other Diseases of the Liver by Laboratory Tests, *J. Lab. & Clin. Med.* **23**:588 (March) 1938.

15. Mateer, J. G.; Baltz, J. I.; Marion, D. F., and MacMillan, J. M.: Liver Function Tests, *J. A. M. A.* **121**:723 (March 6) 1943.

The histologic changes in 4 cases described by Bang and his co-workers^{6b} consist of periportal infiltration, cloudy swelling, vacuolation of hepatic cells and some areas of focal necrosis. It was their impression that the pathologic changes were similar to those seen in infectious hepatitis.

Little attention has been drawn to the hepatic function in non-jaundiced patients with infectious mononucleosis. Mention frequently has been made of enlargement of the liver in this disease (12 per cent in Bernstein's series⁷), but tenderness seldom has been noted. In 1944 Ziegler⁸ reported the observations made at autopsy in a case of infectious mononucleosis in a young woman who died of a ruptured spleen. Before death, the liver was palpable and tender but there was no jaundice. The microscopic changes noted were similar to those described^{6a, b} as seen in jaundiced patients.

Recently, Cohn and Lidman⁹ reported serial tests of hepatic function in 15 consecutive cases of infectious mononucleosis, in none of which was there jaundice. Every patient had definite evidence of impaired hepatic function that persisted for periods of three to eight weeks. One patient, not included in the series, had a persistence of hepatic damage and was considered to have chronic hepatitis on the basis of infectious mononucleosis. The authors felt that diet, vitamin therapy and rest shortened the course of the disease.

At the time that the aforementioned article appeared we had begun a similar study. In the present report it is further shown that hepatic involvement occurs in the great majority of cases of infectious mononucleosis.

MATERIAL AND METHODS

Serial tests of hepatic function were performed in 19 consecutive cases of infectious mononucleosis observed by us between January and August 1946. None of the patients had jaundice. The subjects consisted of 16 students from the professional schools at Northwestern University, 2 private patients and 1 clinic patient. The diagnosis of the disease was based on the usual criteria, namely, the clinical picture, the presence of atypical lymphocytes in the blood and a positive reaction to the heterophile antibody test in serum dilutions of 1 to 160 or over. Since many more cases were encountered in students during the first half of 1946 than in the same period in previous years a mild epidemic was considered to have occurred. A number of students were thought to have an extremely mild form of the disease, but since evidence in favor of a diagnosis of infectious mononucleosis was equivocal they were not included in this study. It was not always possible to make tests of hepatic function as often or for as long a period as was desired, since many of the students went home soon after the diagnosis was made or left school for summer vacations.

7. Bernstein, A.: Infectious Mononucleosis, *Medicine* **19**:85 (Feb.) 1940.

8. Ziegler, E. E.: Infectious Mononucleosis: Report of a Fatal Case with Autopsy, *Arch. Path.* **37**:196 (March) 1944.

9. Cohn, C., and Lidman, B. I.: Hepatitis Without Jaundice in Infectious Mononucleosis, *J. Clin. Investigation* **25**:145 (Jan.) 1946.

Hepatic Function in Nineteen Patients with Infectious Mononucleosis

Case; Sex; Age	Date (Approximate Onset of Symptoms in Parenthesis)	Heterophile Aggluti- nation, Dilution	Icterus Index, Units	Cephalin- Cholesterol Flocculation			Retention of Sulfobromophthalein, per Cent			Serum Albumin, Gm. per 100 Cc.	Serum Globulin, Gm. per 100 Cc.	Liver *	Spleen *	Symptoms
				24 Hr.	48 Hr.		30 Min.	45 Min.	60 Min.					
1 M 20 yr.	(12/25/45)													
	1/10/46	1:320	8	6	..	3.7	3.4	0	T	Mild
	1/24/46	1:320	8	12	..	5.1	3.1	P	0	P
	4/16/46	P	0	P
	5/24/46	0			
2 M 20 yr.	6/12/46	1:10	7	0	0	..	4					
	(2/25/46)													
	2/25/46	1:2,560	10	++++	21	..	5.0	2.8	P	T	Mild
	3/ 8/46	8	++++	4	..	4.6	2.6	P	T	P
	3/11/46	6	++++	P	T	P
3 M 22 yr.	3/19/46	P	T	P
	3/22/46	P	T	P
	3/26/46	P	T	P
	3/25/46	1:2,560	10	2	P	T	P
	4/ 3/46	9	++++	0	P	0	0
4 M 6 yr.	4/16/46	1:1,280	..	++++	++	P	0	0
	6/23/46	++++	++	P	0	0
	6/24/46	0	+	P	0	0
	(2/24/46)		0	0	0
	3/15/46	0	0	0
5 M 22 yr.	3/19/46	1:320	5	++++	12	..	4.2	2.8	0	0	Severe
	3/22/46	++++	0	0	0
	3/26/46	++++	8	0	0	0
	5/ 6/46	1:320	..	++	+++	6	0	0	0
	6/23/46	++	+++	0	0	0
6 M 23 yr.	6/24/46	0	+	0	0	0
	(3/ 1/46)		P	0	P
	3/21/46	P	0	P
	4/ 2/46	1:2,560	5	+	+	..	8	..	4	P	0	P
	4/16/46	0	0	..	4	..	0	0	0	0
7 M 27 yr.	4/30/46	++++	++	0	0	Mild
	(3/29/46)		6	++++	++	4	0	0	0
	4/ 2/46	1:2,560	..	++++	++	0	0	0
	4/12/46	1:2,560	..	++++	++	0	0	0
	(4/ 4/46)		..	0	+	0	0	0
8 M 23 yr.	4/ 4/46	1:100	+	..	16	..	4	0	0	Mild
	4/ 9/46	0	0	0
	4/16/46	1:40	7	11	7	P	T	P
	4/23/46	14	10	4.6	2.6	P	T	P
	4/29/46	++++	++	..	8	..	4	P	T	P
9 M 27 yr.	6/10/46	1:2,560	..	++++	++	..	12	..	4	5.3	2.9	0	0	P
	6/ 4/46	++	++	..	12	..	6	0	0	0
	(4/ 5/46)		..	+	+	..	5	..	0	0	0	0
	4/10/46	1:2,560	6	+	+	..	4	..	0	0	0	0
	4/17/46	0	0	0	0	0

* P Indicates palpable and T tender; 0 in the columns headed "Liver" and "Spleen" indicates not palpable or not tender.

COMMENT

According to the report of Cohn and Lidman⁹ and from our own results, it is apparent that impaired hepatic function occurs in practically all cases of infectious mononucleosis. The degree of hepatic damage is seldom sufficient to cause jaundice. The few histologic descriptions of the liver reported in cases of both jaundiced and nonjaundiced patients with mononucleosis uncomplicated by sepsis have revealed the presence of hepatitis.¹⁶ It might then be assumed that hepatitis is almost invariably a pathologic characteristic of infectious mononucleosis.

Involvement of the liver occurs early in infectious mononucleosis, along with changes in the lymph glands and spleen. As enlargement and/or tenderness of the liver were present in 8 of our 19 cases, these signs are considered to be of diagnostic significance. The degree and duration of hepatic damage can be obtained from serial determinations of the cephalin-cholesterol flocculation and from sulfobromophthalein excretion tests. Hepatic insufficiency may subside in a few weeks, or it may persist for months.

Infectious mononucleosis with hepatitis must be differentiated from mild infectious hepatitis without jaundice. In the latter disease there may be adenopathy, splenomegaly and atypical lymphocytes in the blood.¹⁷ The distinguishing feature in infectious mononucleosis is the presence of heterophil agglutinins in high titers; also, the adenopathy, splenomegaly and blood picture are usually more distinctive than in infectious hepatitis.

Because of the possibility of permanent hepatic damage or exacerbations of hepatic dysfunction, the state of the liver should be considered in the management of infectious mononucleosis. Lessons recently learned about the treatment of infectious hepatitis might well be applied to infectious mononucleosis. Probably the most important principle of treatment is rest in bed or decided restriction of activity until hepatic function returns to normal. It is questionable whether an increased intake of protein and carbohydrate alters the course of involvement of the liver in a young person with infectious mononucleosis who has been taking an optimal diet. However, until more evidence is available, such a diet, with vitamin supplements, is advisable. Drugs known to have a toxic effect on the liver (arsenicals, sulfonamide compounds and others) and alcohol are certainly to be avoided. The possible after-effects of this type of hepatitis, such as increased vulnerability of the liver to malnutrition and intoxication, cannot be excluded.

16. Kilham and Steigman.^{9a} Bang and Wanscher.^{9b} Ziegler.⁸

17. Barker, M. H.; Capps, R. B., and Allen, F. W.: Acute Infectious Hepatitis in the Mediterranean Theater, *J. A. M. A.* **128**:996 (Aug. 4) 1945. Hoagland, C. A., and Shank, R. E.: Infectious Hepatitis: A Review of Two Hundred Cases, *ibid.* **130**:615 (March 9) 1946.

Reactions to the initial tests of hepatic function, made from one to twenty-four days after the onset of symptoms, were positive in 17 patients. Thereafter the degree of hepatic dysfunction regressed, and 12 cases were followed until the tests yielded normal results. There seemed to be some correlation between the severity of symptoms and the degree of hepatic damage. Five patients (cases 10, 11, 12, 16 and 18) who had high fever and prostration for five to seven days all had rather high retention of dye. In 7 patients (cases 5, 7, 8, 9, 14, 15 and 19), who had a mild type of infectious mononucleosis with only slight or no fever and malaise, hepatic dysfunction was minimal. The presence of hepatic involvement might be questioned in cases 7 and 9, but it is indicated by the return to normal of the cephalin-cholesterol flocculation from a 2 plus and 3 plus reaction.

The average duration of disease of the liver, as shown by tests of hepatic function, was from two to six weeks. An unusually long period of hepatic involvement occurred in cases 1, 2 and 3, in which the reactions to test of hepatic function remained positive for four and one half, three and two months respectively. The first 2 patients had mild attacks of infectious mononucleosis, while the third patient was decidedly ill and had fever for about three weeks. These and other patients in the series felt comparatively well before the reactions to the tests of hepatic function became negative.

The occurrence and duration of enlargement and tenderness of the liver and of splenomegaly are shown in the table. The liver was palpable in 7 cases and continued to be so for varying periods. Tenderness over the region of the liver occurred at some time in 7 patients; in 2 of these the liver was not palpable at the time when it was tender. Tenderness was usually transient, but it persisted for two weeks in case 6 and for four weeks in case 2. The spleen was palpable in 12 cases (63 per cent). Three patients (cases 1, 2 and 6) who had a persistence of splenomegaly for one to four months also had a prolonged period of hepatic involvement.

All the patients in this series were given rest in bed until their temperature returned to normal. In addition, they were given a high protein, high carbohydrate diet, dried yeast powder and multivitamin preparations. We have no evidence that the course of the disease was altered by the dietary regimen or by the vitamin supplements. Most of the patients resumed moderate activity, such as going to classes, before the hepatic function had returned to normal. There was no correlation in this group between subjective symptoms and the persistence of hepatic damage; some felt well, while others had malaise and easy fatigability. None of the patients had a relapse of hepatic disease as indicated by tests of hepatic function or by an increase in the size of the liver.

AORTIC STENOSIS WITH ELEVATED METABOLIC RATE SIMULATING HYPERTHYROIDISM

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ONE OF the most gratifying experiences in the care of patients suffering from cardiovascular disease is the treatment of patients with thyrocardiac disease. This is true whether the cardiac disability is entirely due to thyrotoxicosis or whether there is an additional independent cardiac lesion. Such patients respond so well to proper management and often have so few of the customary signs of thyrotoxicosis that physicians have been impelled to search carefully for these cases of masked thyrotoxicosis. The result is that on minor suspicion determinations of basal metabolism are frequently performed in order not to overlook thyrotoxicosis as a remediable burden in patients suffering from various types of cardiac disability. At times the decision is difficult, because there are numerous other causes of an elevated basal metabolism apart from hyperthyroidism. Peabody and Wentworth¹ pointed out that cardiac failure itself caused an increase in consumption of oxygen and estimated that if the vital capacity fell below approximately 60 per cent of normal further degrees of failure would cause an increase in metabolism roughly proportional to the degree of failure. Hamburger and Lev,² Shapiro³ and Resnick and Friedman⁴ confirmed these observations, and it was suggested that the cause of the increased basal metabolic rate in cardiac failure was largely the muscular effort

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1. Peabody, F. W.; Wentworth, J. A., and Barker, B.: Clinical Studies on the Respiration: The Basal Metabolism and the Minute-Volume of the Respiration of Patients with Cardiac Disease, *Arch. Int. Med.* 20:468 (Sept.) 1917.

2. Hamburger, W. W., and Lev, M. W.: Basal Metabolism in Organic Heart Disease with Congestive Failure, *J. A. M. A.* 84:587 (Feb. 21) 1925.

3. Shapiro, S.: The Basal Metabolic Rate in Cases of Chronic Cardiac Disease and in Cases of Hypertension, *Arch. Int. Med.* 38:385 (Sept.) 1926.

4. Resnick, H., Jr., and Friedman, B.: Studies on the Mechanism of the Increased Oxygen Consumption in Patients with Cardiac Disease, *J. Clin. Investigation* 14:551 (Sept.) 1935.

SUMMARY

In 19 consecutive cases of infectious mononucleosis without jaundice varying degrees of hepatic dysfunction were present. This was shown by serial cephalin-cholesterol flocculation and sulfobromophthalein excretion tests. The duration of hepatic involvement ranged from two weeks to five months. Enlargement and tenderness of the liver were common physical findings.

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crackling rales were heard at the bases. The heart was enlarged, the rhythm was regular and a palpable systolic thrill was felt at the base. A loud systolic and a blowing diastolic murmur were heard at the base. At the apex the diastolic murmur had a rumbling quality. The blood pressure was 130 systolic and 80 diastolic; the liver was not enlarged, and there was no pitting edema. There was no tremor of the fingers. The Hinton test of the blood gave a negative reaction, and repeated examinations of the sputum showed no tubercle bacilli. The electrocardiogram showed left axis deviation. Roentgenologic examination showed pulmonary congestion, enlargement of the left ventricle and left auricle and calcification of both the aortic and the mitral valves.

The clinical diagnosis was rheumatic aortic and mitral stenosis with congestive heart failure. The patient responded favorably to digitalis and diuretic therapy. On the fourteenth and seventeenth days of her stay, when she was comfortable and much improved, the basal metabolic rate was found to be $+35$ and $+37$ per cent respectively.

The question of thyrotoxicosis was debated but remained in doubt. It was decided that an operation should be performed, in the belief that even if the gland proved to be normal some help might be obtained. However, after transfer of the patient to the surgical service fever developed, and she had a rapidly downhill course and died without an operation being performed.

Postmortem examination revealed chronic rheumatic heart disease, with aortic and mitral stenosis, bronchopneumonia and pulmonary thrombosis. The weight of the heart was 580 Gm. The thyroid gland was normal both grossly and microscopically.

Comment.—The loss of 15 pounds (6.8 Kg.) in weight and the slight exophthalmos, palpable thyroid, moist skin and elevated metabolic rate, at a time when the patient was not dyspneic and showed little congestion, all suggested thyrotoxicosis, but the thyroid gland was normal.

CASE 2.—A 51 year old painter entered the hospital on May 7, 1934, complaining of increasing breathlessness, especially at night. He had a history of an old peptic ulcer, and roentgenologic examination had previously shown an active duodenal ulcer. There was no history of rheumatic fever. About two years before his admission to the hospital he had definite anginal pain on walking and slight breathlessness. Later, typical attacks of paroxysmal nocturnal dyspnea developed. Some years ago he had weighed 202 pounds (98 Kg.), and this weight had steadily fallen to 150 pounds (68 Kg.), though until recently he had had a voracious appetite.

The skin was moist. There was no exophthalmos, and the thyroid was not enlarged. The heart was considerably enlarged; the rhythm was regular, and there were a loud, harsh aortic systolic murmur and a faint diastolic blow. A definite systolic thrill was felt at the base. At the apex both a loud systolic and a faint mid-diastolic murmur were heard. The blood pressure was 114 systolic and 54 diastolic. Moist rales were heard at the bases of the lungs, and the liver was definitely enlarged. There was no pitting of the ankles.

The electrocardiogram revealed left bundle branch block; the Hinton test gave a negative reaction, and the blood cholesterol content was 186 mg. per hundred cubic centimeters. A roentgenogram of the chest on the patient's twenty-first day in the hospital showed calcification of the aortic valve and calcification of a coronary artery. At that time there was no pulmonary congestion. Four determinations of basal metabolism were made, on the tenth, eleventh, thirteenth and seventeenth days of his stay, and the rates were $+48$, $+53$, $+34$ and $+38$ per cent respectively. These were all taken when dyspnea and pulmonary congestion were absent. The vital capacity during these days was around 2,500 cc.

involved in dyspnea. Riesman⁵ called attention to the fact that hypertension of itself was capable of simulating hyperthyroidism in some instances, and Boas and Shapiro⁶ substantiated this clinical observation with determinations of basal metabolic rate in a series of hypertensive patients, stating that this syndrome most frequently occurred in those having appreciable elevation of both systolic and diastolic levels. There are additional conditions in which the metabolism may be somewhat elevated, such as polycythemia,⁷ leukemia,⁸ pregnancy,⁹ coarction of the aorta¹⁰ and cardiac failure associated with beriberi.¹¹ Apart from these, fever, severe anemia and emotional excitement can produce an elevation in the metabolic rate, and no doubt there are still other disorders in which the metabolism is elevated.

We have been confronted with a group of patients with aortic stenosis and well marked elevations in metabolic rate in whom the degree of cardiac failure was too slight to account for these elevations. The patients also showed clinical features resembling thyrotoxicosis and yet had normal thyroid glands. The purpose of this communication is to report 4 authenticated cases of such a syndrome.

REPORT OF CASES

CASE 1.—A woman entered the hospital on Nov. 29, 1933, complaining of choking cough, weakness and dyspnea of ten months' duration. She had had attacks of rheumatic fever in childhood and early adult life. She had lost 15 pounds (6.8 Kg.) during the previous year. Ten months before her admission to the hospital she contracted a severe respiratory infection, with a productive cough. This was followed by increasing dyspnea, weakness and spasmodic attacks of coughing. Three months before her admission she coughed up a cupful of bright blood and had to quit her work. Her appetite was poor, and she steadily grew worse.

Examination showed a slightly cyanotic, moist skin. There was slight lid-lag but no exophthalmos. The thyroid was palpable and was regarded as slightly enlarged. The chest was hyperresonant; expiration was prolonged, and a few

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9. Root, H. F., and Root, H. K.: The Basal Metabolism During Pregnancy and the Puerperium, *Arch. Int. Med.* **32**:411 (Sept.) 1923. Sanderford, I., and Wheeler, T.: The Basal Metabolism Before, During and After Pregnancy, *J. Biol. Chem.* **62**:329 (Dec.) 1924.

10. Blackford, L. M.: Coarctation of the Aorta, *Arch. Int. Med.* **41**:702 (May) 1928.

11. Okada, S.; Sakurai, E.; Ibuki, T., and Kabeshima, H.: Basal Metabolism in Vitamin B Starvation, *Arch. Int. Med.* **40**:292 (Sept.) 1927.

pneumonia and pulmonary infarction. The residual thyroid tissue was normal grossly and microscopically.

Comment.—This patient with rheumatic aortic and mitral stenosis had a definitely elevated basal metabolic rate at a time when there was little objective evidence of congestion and practically no dyspnea. A slight elevation in basal metabolic rate persisted even after removal of nine tenths of the gland. Both the surgical specimen and the autopsy material showed normal thyroid tissue.

CASE 4.—A 57 year old woman entered the hospital on Feb. 20, 1944, complaining of shortness of breath of two and a half years' duration and increasing weakness. There was no history of rheumatic fever. Her present illness was precipitated when she ran for a streetcar, at which time she became breathless and then fainted, and she had been invalided ever since, remaining in bed a good deal of the time. Dyspnea progressed, and she noticed pain in the chest radiating down both arms on effort.

Examination showed the skin to be warm and moist. There was no exophthalmos or lid-lag; the thyroid was not enlarged. There was slight tremor of the fingers. The heart was somewhat enlarged; the rhythm was regular, and there was a grade 3 aortic systolic murmur. No diastolic murmurs were heard. No thrills were felt. There was alternation of the radial pulse and also of the intensity of the systolic murmur. The blood pressure was 110 systolic and 90 diastolic. The lungs showed rales and a slight amount of fluid at the bases. The liver was possibly somewhat enlarged, and there was no pitting edema.

Roentgenologic study revealed an old tuberculous lesion of the upper lobe of the right lung, considerable pulmonary congestion, slight hydrothorax on the left side and a calcified mass in the region of the aortic valve. One week later a roentgenogram showed disappearance of the pulmonary congestion and the pleural fluid. The blood urea nitrogen content was 15 mg. and the blood cholesterol level was 298 mg. per hundred cubic centimeters. The electrocardiogram showed intraventricular block, with a normal sinus rhythm. The basal metabolic rate was +38, +39, +41 and +42 per cent on the ninth, sixteenth, eighteenth and twentieth days in the hospital respectively.

The patient improved satisfactorily on administration of digitalis, mercury diuretics and a salt-free diet. Therapy with strong solution of iodine was started on the thirteenth day and continued thereafter. She showed no obvious evidence of cardiac failure after the sixth day of her stay in the hospital. On the twenty-third day a subtotal thyroidectomy was performed, with the removal of seven eighths of the gland. Just as the operation was finished she went into collapse, the blood pressure fell and she died suddenly. Histologic examination of the gland revealed it to be entirely normal, five different sections having been examined. Permission for autopsy was not obtained.

Comment.—This patient had undoubted aortic stenosis, as evidenced by the physical findings and the detection of aortic valvular calcification by fluoroscopy. She had a persistent elevation of the basal metabolic rate, in the region of +40 per cent, at a time when pulmonary congestion and dyspnea were insignificant. This was not influenced by iodine therapy. Though permission for postmortem examination was not obtained, most of the thyroid gland was removed at operation and found to be normal.

The 4 patients in this report had calcific aortic stenosis, and 2 also had mitral stenosis. The main point of interest is that they all showed decided elevation of the basal metabolic rate on repeated examination at times when there was little if any dyspnea or pulmonary congestion.

The patient's clinical condition improved considerably on administration of digitalis and mercurial diuretics. The diagnosis was calcific aortic stenosis, with slight insufficiency, angina pectoris and coronary sclerosis. Because of the possibility of thyrotoxicosis, administration of 10 drops of strong solution of iodine U.S.P. three times daily was started on the fourteenth day of his stay and continued thereafter. The basal metabolic rate appeared to fall somewhat with the patient on iodine therapy. He was transferred to the surgical service, though it was not certain whether he had thyrotoxicosis. It was planned at that time to perform a total thyroidectomy. The day before the scheduled operation, while sitting in bed, he reached for a glass of water and died instantly.

Postmortem examination showed an enlarged heart, weighing 640 Gm. The aortic valve was strikingly calcified and stenosed, and there were multiple old small healed myocardial infarctions, calcified coronary arteries and a healed duodenal ulcer. The thyroid gland was grossly and microscopically normal.

Comment.—This patient with calcific stenosis and angina pectoris had several features suggestive of thyrotoxicosis. There was much loss of weight, with a good appetite, and a decided elevation of the basal metabolic rate, which persisted when he was well compensated and which fell definitely when he was on iodine therapy. Despite this, the thyroid gland was normal.

CASE 3.—A woman 69 years old first entered the hospital on May 31, 1933. She had had rheumatic fever at the age of 19 and diabetes since the age of 60. In 1929 she had a nervous breakdown and was sick for several months. The usual weight was 148 pounds (67 Kg.), but within about a year it had fallen to 108 pounds (49 Kg.). A year before her admission to the hospital she first had sudden dyspnea while carrying some packages and had been short of breath on slight effort ever since.

Examination showed that the skin was moist, the eyes were not prominent and the thyroid was not palpable. The heart was somewhat enlarged, the rhythm was regular and a grade 4 systolic murmur was heard in the aortic area and less well heard over the precordium. No diastolic murmurs could be heard anywhere. The apical first sound was accentuated. The blood pressure was 160 systolic and 90 diastolic. The lungs showed scattered coarse rales; the liver was not palpable, and there was no peripheral pitting. There was a slight tremor of the fingers.

Laboratory examination showed a blood sugar content of around 200 mg. and a blood urea nitrogen level of 8 mg. per hundred cubic centimeters. An electrocardiogram showed left axis deviation with normal sinus rhythm. A roentgenogram of the chest showed cardiac enlargement, with a calcified mass in the region of the aortic valve and slight pulmonary congestion. The urine contained an occasional trace of albumin and sugar. The basal metabolic rate was +31, +46 and +29 per cent on the second, third and ninth days in the hospital.

Clinically, the patient improved on digitalis and insulin therapy. Because of the possibility of thyrotoxicosis in addition to rheumatic heart disease, administration of strong solution of iodine was started on the fourth day, and ten days later a subtotal thyroidectomy was performed, with procaine hydrochloride anesthesia. About nine tenths of the gland was removed. The patient left the hospital improved. Pathologic examination of the specimen of thyroid removed revealed a normal gland. Her subsequent course was not satisfactory. In October 1933 the basal metabolism on two occasions was +19 and +22 per cent, despite the previous removal of nine tenths of the thyroid gland. Later, congestive failure became more prominent and refractory to therapy, and the patient died on Jan. 25, 1935.

Postmortem examination showed calcified rheumatic stenosis of the mitral and aortic valves. The weight of the heart was 420 Gm. The lungs showed broncho-

TREATMENT OF ALLERGY TO INSULIN WITH DIPHENHYDRAMINE HYDROCHLORIDE

Report of Two Cases

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INTRODUCTION

Antigenic Nature of Insulin.—Insulin has been proved to be a complete and soluble protein, and like other proteins¹ it may act as an antigen. Precipitins and complement fixation antibodies probably are formed in the susceptible organism after the injection of insulin,² but this opinion is not universally accepted. Reagins (circulating antibodies responsible for dermal reactions) frequently can be demonstrated in persons sensitive to insulin by passive transfer.³

Chemists have been unable to find any difference in the microscopic appearances, isoelectric points, solubilities and molecular formulas of crystalline insulins from such varying sources as the ox, sheep, hogs and fish.³ Some workers have maintained that the insulin derived from the pancreases of human beings, cattle, hogs, sheep, bison and dogs has an immunologic identity.⁴ Other immunologists have found that beef and pork insulins have antigenic activity in common and also have a "residuum of specificity to the species."⁵

It is difficult to reconcile this evidence of the similarity of animal and human insulin with the allergy which some persons exhibit toward beef

This work was done under the direction of Dr. C. F. Code and Dr. R. M. Wilder, with the cooperation of Dr. William Locke.

1. Jensen, H.: The Chemical Study of Insulin, *Science* **75**:614-618 (June 10) 1932.

2. Harten, M., and Walzer, M.: Allergy to Insulin, Liver, Pituitary, Pancreas, Estrogens, Enzymes and Similar Substances, *J. Allergy* **12**:72-108 (Nov.) 1940.

3. Scott, D. A.: Further Studies on Crystalline Insulin, *J. Biol. Chem.* **92**: 281-288 (July) 1931.

4. Wasserman, P., and Mirsky, I. A.: Immunological Identity of Insulin From Various Species, *Endocrinology* **31**:115-118 (July) 1942.

5. Lewis, J. H.: Antigenic Properties of Insulin, *J. A. M. A.* **108**:1336-1338 (April 17) 1937.

Despite this, the thyroid gland was grossly and microscopically normal in all cases. Each case presented some of the other clinical features suggestive of thyrotoxicosis, such as pronounced loss of weight, moist skin, slight tremor of the fingers, slight enlargement of the thyroid and exophthalmos. In none did a striking decrease in metabolism on administration of strong solution of iodine occur, though a slight fall was observed. It is of interest that in all 4 instances the heart beat was regular though congestive failure had been present, when ordinarily auricular fibrillation with cardiac failure is expected in thyrotoxicosis. It must be emphasized that these patients displayed as much apparent clinical evidence of thyrotoxicosis as many others we have seen who were proved to have a toxic thyroid gland.

The cause of the elevated metabolic rate in these patients remains obscure. It has been suggested that the increased weight of the heart (500 Gm.) of itself can increase the basal metabolic rate to as high as +20 per cent even in the absence of congestive failure, because of increased consumption of oxygen of the cardiac muscle.⁴ This explanation does not appear to be satisfactory, as an analysis of 7 other random cases of aortic stenosis coming to autopsy failed to confirm this observation. The average weight of the heart in this group was 533 Gm., and the average basal metabolic rate was +3 per cent. The readings in metabolism, in fact, ranged from a low of -4 to a high of +12 per cent. To be sure, some of these patients may normally have had the low metabolic rate of hypothyroidism, and a slight increase may have developed as a result of cardiac hypertrophy.

The inference from this study is that there are some patients with aortic stenosis, with or without mitral stenosis, who have a persistent elevation of the basal metabolic rate even when dyspnea and pulmonary congestion are inconspicuous or absent, and who may also show other clinical evidence suggesting hyperthyroidism, but have a normal thyroid gland. It is suggested that determination of protein-bound iodine as a measure of thyroid function may prove helpful in a differential diagnosis. Such determinations were not made in this study.

CONCLUSION

Four cases of aortic stenosis without significant pulmonary congestion or dyspnea are reported in which the patients showed definite and persistently elevated basal metabolic rates and had normal thyroid glands grossly and microscopically. They also manifested some of the other features suggestive of thyrotoxicosis. This adds another group of conditions that needs to be considered in the differential diagnosis of masked thyrocardiac disease.

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Tenderness and pruritus may be present. Tuft considered that such mild symptoms do not depend on an antigen-antibody reaction.¹¹

The severe local reaction consists of the same redness, swelling, pruritus, tenderness and even local heat, in greater degree. The involved region may reach 5 to 8 cm. in diameter, and then the reaction subsides within a week. Local reactions usually are observed between the third and fourteenth days after injections of insulin are begun. It is uncommon to experience a reaction with the first injection unless insulin has been used previously. Usually if insulin has been used continuously for two weeks without symptoms no difficulty will occur.

The generalized reaction may manifest itself in a variety of ways. A cutaneous reaction is the most common and usually consists of urticaria and angioneurotic edema or rarely of generalized dermatitis. Laryngeal edema may cause some degree of respiratory obstruction, but no death, to our knowledge, has been reported as the immediate result of sensitivity to insulin.² Circulatory symptoms of pallor, flushing and palpitation may be followed by some degree of shock. Gastrointestinal symptoms of nausea, vomiting and abdominal cramps may occur. Severe symptoms usually disappear within an hour or two, but discomfort from the urticaria may persist for days. The similarity to serum sickness in symptoms and in time of onset (usually about ten days after treatment is begun) has been noted by others.²

Rarely allergy to insulin may be associated with refractoriness to insulin. Lowell¹² found evidence of two distinct antibodies in an instance of refractoriness, one responsible for dermal sensitivity and the other neutralizing the hypoglycemic effects of insulin.

A single instance of exaggerated physiologic response to insulin (hypoglycemia) has been reported as a manifestation of allergy. This manifestation responded to desensitization.¹³

Incidence of Hypersensitivity to Insulin.—Statistics vary greatly, but of the patients receiving insulin, approximately 1 in 10 will experience mild, local reactions, and only 1 in 1,000 will have a systemic reaction.¹⁴ Goldner and Ricketts¹⁵ found only 23 reported instances of generalized sensitivity to crystalline insulin confirmed by allergy studies.

11. Tuft, L.: Insulin Hypersensitiveness: Immunologic Considerations and Case Reports, *Am. J. M. Sc.* **176**:707-720 (Nov.) 1928.

12. Lowell, F. C.: Evidence for the Existence of Two Antibodies for Crystalline Insulin, *Proc. Soc. Exper. Biol. & Med.* **50**:167-172 (May) 1942.

13. Stötter, G.: Desensibilisierungserfolg bei einem hochgradig insulinallergischen Diabetiker, *Klin. Wchnschr.* **16**:1180-1183 (Aug. 21) 1937.

14. Yasuna, E.: Generalized Allergic Reactions to Insulin: Review of Literature, with Report of Case, *J. Allergy* **12**:295-306 (March) 1941. Allan and Scherer.⁷

15. Goldner, M. G., and Ricketts, H. T.: Insulin Allergy: Report of Eight Cases with Generalized Symptoms, *J. Clin. Endocrinol.* **2**:595-602 (Oct.) 1942.

or pork insulin. If the commercial insulin derived from pork or beef is identical with a person's own insulin, then the paradoxical state of hypersensitivity to his own hormones exists. Zondek and Bromberg⁶ have given evidence that sensitivity to endogenous steroid hormones may occur, and this hypothesis cannot entirely be discarded in considering allergy to insulin, particularly in cases in which it is associated with diabetes and an insulin refractory state. Other workers⁷ have maintained that it is obviously impossible to become sensitive to one's own hormones and have suggested other explanations, such as impurities in the crystalline insulin. This last view has received at least partial confirmation from the work of Hansen and Eyer,⁸ who found that recrystallized commercial crystalline zinc insulin gave less severe reactions than did the original crude crystalline form. Another possibility is that the molecular structure of animal insulin is similar enough to that of human insulin to be active in the promotion of carbohydrate metabolism and yet dissimilar enough to act as an antigen.

Insulin modifiers, such as globin and protamine, have been implicated. Page and Bauman⁹ found that there were more than seven times as many reactions to the protein, protamine, as to globin. They also found, however, that desensitization to protamine takes place easily. Harten and Walzer² considered that positive cutaneous reactions to protamine zinc insulin are always associated with positive reactions to other insulins, such as beef, pork and crystalline insulins. Cohen and Simon¹⁰ implied that protamine zinc insulin causes more reactions than regular insulin.

Types of Hypersensitivity to Insulin.—Allan and Scherer⁷ described three classes of reactions: the mild local reaction, the severe local reaction and the generalized reaction. To these may be added the allergy associated with a diminished, and that associated with an exaggerated, response to insulin.

The mild local reaction consists of a stinging sensation at the time of injection, followed by swelling and redness in an area 1 to 4 cm. in diameter, which appear an hour or two later, reach maximal intensity twelve to twenty-four hours later and disappear in one to three days.

6. Zondek, B., and Bromberg, Y. M.: Endocrine Allergy: I. Allergic Sensitivity to Endogenous Hormones, *J. Allergy* **16**:1-16 (Jan.) 1945.

7. Allan, F. N., and Scherer, L. R.: Insulin Allergy, *Endocrinology* **16**:417-430 (July-Aug.) 1932.

8. Hansen, K., and Eyer, H.: Klinische Studien über allergische Krankheiten: V. Insulin-Allergie, *Deutsches Arch. f. klin. Med.* **174**:133-142 (Oct.) 1932.

9. Page, R. L., and Bauman, L.: Insulins and Insulin Modifiers: Intradermal Studies, *J. A. M. A.* **124**:704-705 (March 11) 1944.

10. Cohen, A. E., and Simon, F.: Insulin Hypersensitivity, *J. Allergy* **9**:503-508 (July) 1938.

Miscellaneous Factors in Local Reactions.—In addition to the insulin itself, other factors may be responsible for the reaction. Animal protein or some other substance from the pancreas not removed in extraction may be present, but commercial insulins are considered to have a nitrogen content "practically the same"² as that of crystalline insulin. The alcohol in which the syringe is kept may be responsible for an irritation which appears within a few minutes after injection and subsides within an hour.⁷ The preservative in the insulin and the denaturing materials, particularly solution of formaldehyde, and the alcohol used for cleansing the skin may cause reaction.²³

PROCEDURES USED AND CASES STUDIED

Sensitivity of the skin to insulin and a measure of the effectiveness of treatment with diphenhydramine hydrochloride were determined by measuring the sizes of the flares following intracutaneous injections. Skin-testing procedures were performed in a room maintained at a temperature of 78 F. and at a relative humidity of 40 per cent. Various dilutions of a commercial crystalline zinc insulin U-40 (Lilly) in isotonic solution of sodium chloride were prepared daily for use in testing. A series of testing and control solutions were injected intracutaneously, and colored photographs of the cutaneous reactions were made at intervals of five to ten minutes. The photographs were then projected in actual size, their outlines traced and the areas of the flares accurately determined in square centimeters by means of a planimeter. The maximal size attained by each flare was considered to be the measurement of greatest significance and is recorded in the accompanying tables.

CASE 1.—A white man, 71 years of age at the time of the present study, experienced his first symptoms of allergy at the age of 16 years, when he had several attacks of respiratory difficulty suggestive of asthma. In 1929, without obvious cause, he had an episode of severe urticaria and angioneurotic edema. Since then, at intervals of two to three years, he has had similar, milder attacks, but no etiologic factor has been discovered.

In 1936, at the age of 61 years, the patient noted the gradual onset of polydipsia, polyuria and loss of weight. In 1937 glycosuria and hyperglycemia were discovered, and a diagnosis of diabetes mellitus was established. He was given 10 units of protamine zinc insulin daily, but within a few weeks he found that itching, burning, redness and swelling were appearing at the sites of injection. However, when the insulin was injected into the abdominal wall rather than in the thighs no further difficulty was experienced. (This occurrence is noted frequently in patients with diabetes.) After two months of treatment with insulin, all glycosuria had disappeared and diet alone was sufficient to control the diabetes.

From 1937 to 1946 the diet was restricted moderately and the patient had no glycosuria.

In March 1946, polydipsia, polyuria and glycosuria reappeared. The glycosuria failed to respond to regular insulin in amounts up to 120 units daily, and the patient

23. Cohen and Simon.¹⁰ Harten and Walzer.²

Treatment of Hypersensitivity to Insulin.—Desensitization with insulin has been used effectively in treatment of hypersensitivity to insulin.¹⁶ In this method, increasing amounts of insulin are administered until therapeutic doses are reached. This is required so seldom that no standardized method has been adopted. In a few of the reported cases the initial dose varied from 0.0001 to 1.0 unit, the time required from one to fourteen days and the interval between injections from twenty minutes to twenty-four hours.¹⁷

In the treatment of mild, local reactions it is usually sufficient to continue the daily injections in spite of symptoms. Such reactions usually diminish or entirely disappear after several weeks.

Changing from one brand of insulin to another and changing from beef to pork insulin or to crystalline insulin are methods of treatment frequently suggested, but conclusive evidence of their effectiveness is rarely presented. Sensitivity to pork insulin but not to beef insulin was verified by skin tests in 1 case by Cohen and Simon.¹⁰

Histamine desensitization has been used successfully in treatment of hypersensitivity to insulin.^{17b} The initial dose of histamine phosphate is 0.002 mg. subcutaneously; injections are made twice daily,¹⁸ and amounts are increased as tolerated. Favorable results from the administration of histaminase were reported by Roth and Horton.¹⁹ Best and McHenry,²⁰ however, stated that no clinically effective preparation is available. The serum of a rabbit sensitized to the patient's serum was used once successfully.²¹

We have recently published studies of a case in which generalized urticaria was a manifestation of allergy to insulin and the response to diphenhydramine hydrochloride, or "benadryl hydrochloride," was satisfactory.²² Two similar cases will be described in the present article.

16. Weitz, M. A.: Insulin Hypersensitivity with Desensitization: Report of a Case, *J. Allergy* **14**:220-226 (March) 1943.

17. (a) Corcoran, A. C.: Note on Rapid Desensitization in Case of Hypersensitiveness to Insulin, *Am. J. M. Sc.* **196**:359-361 (Sept.) 1938. (b) Collens, W. S.; Lerner, G., and Fialka, S. M.: Insulin Allergy: Treatment with Histamin, *Am. J. M. Sc.* **188**:528-533 (Oct.) 1934. Weitz.¹⁶ Harten and Walzer.²

18. Roth, G. M., and Rynearson, E. H.: Use of Histamine and Histaminase in Treatment of Allergic Reaction to Insulin, *Proc. Staff Meet., Mayo Clin.* **14**:353-357 (June 7) 1939.

19. Roth, G. M., and Horton, B. T.: Histaminase: Physiologic Effects on Man and Its Therapeutic Value in Medicine, *Bull. New York Acad. Med.* **16**:570-584 (Sept.) 1940.

20. Best, C. H., and McHenry, E. W.: A Note on Histaminase, *J. A. M. A.* **115**:235-236 (July 20) 1940.

21. Karr, W. G.; Scull, C. W., and Petty, O. H.: Insulin Resistance and Sensitivity, *J. Lab. & Clin. Med.* **18**:1203-1211 (Sept.) 1933.

22. Gastineau, C. F., and Leavitt, M. D.: Treatment of Allergy to Insulin with Benadryl: Report of One Case, *Proc. Staff Meet., Mayo Clin.* **21**:316-319 (Aug. 21) 1946.

When the patient was dismissed from the clinic, glycosuria was controlled in a satisfactory manner by the administration of a mixture of 30 units of protamine zinc insulin and 60 units of regular insulin before breakfast and 30 units of regular insulin before the evening meal. In spite of this high requirement of insulin, it was felt that the patient had rather mild diabetes because acetonuria was minimal and the levels of fasting blood sugar did not exceed 200 mg. per hundred cubic centimeters when insulin was omitted.

CASE 2.—A woman 50 years old came to the Mayo Clinic in February 1946 because of recurrent abdominal pain. In 1942 glycosuria had been discovered

TABLE 3.—*Direct Skin Tests with Mixtures of Crystalline Insulin and Diphenhydramine Hydrochloride*

Solutions Injected	Amount, Cc.		Maximal Size of Flare, Sq. Cm.		Reduction in Size of Flare, %
Case 1					
Insulin U-40.....	0.1	}	21.2	}	75.5
Isotonic solution of sodium chloride.....	0.1				
Insulin U-40.....	0.1	}	5.2		
Diphenhydramine hydrochloride 1:1,000.....	0.1				
Insulin 1:10.....	0.1	}	17.0	}	75.9
Isotonic solution of sodium chloride.....	0.1				
Insulin 1:10.....	0.1	}	4.1		
Diphenhydramine hydrochloride 1:1,000.....	0.1				
Insulin 1:100.....	0.1	}	12.9	}	100.0
Isotonic solution of sodium chloride.....	0.1				
Insulin 1:100.....	0.1	}	0		
Diphenhydramine hydrochloride 1:1,000.....	0.2				
Isotonic solution of sodium chloride.....	0.2		0		
Diphenhydramine hydrochloride 1:1,000.....	0.2		0		
Case 2 *					
Insulin 1:5,000.....	0.1	}	17.0	}	81.8
Isotonic solution of sodium chloride.....	0.1				
Insulin 1:5,000.....	0.1	}	3.1		
Diphenhydramine hydrochloride 1:1,000.....	0.1				
Isotonic solution of sodium chloride.....	0.2		0		
Diphenhydramine hydrochloride 1:1,000.....	0.2		0		

* Because of the previous severe reaction (generalized urticaria) in case 2 to larger amounts of insulin, only a single injection of insulin in a 1:5,000 dilution was employed in this study.

after a period of loss of weight, polyuria and polydipsia. The patient was given regular insulin and later protamine zinc insulin, but because of increasing local burning, pruritus and redness, use of insulin was discontinued after three months. No difference between the effects of the two insulins was noted. Glycosuria then was controlled by diet until 1943, when she had a miscarriage. She received protamine zinc insulin, with increasingly severe local reactions, for nine days, when a "clear" insulin (probably regular) was substituted. After four days, generalized urticaria and angioneurotic edema appeared, and the patient remained extremely uncomfortable for five days. Glycosuria was controlled by diet until registration at the clinic in February 1946.

The chief complaint was recurrent abdominal pain, and examination revealed that cholecystectomy was necessary immediately. Therefore an estimate of the

complained bitterly of an indefinite feeling of malaise. No local reactions were noted at this time. The malaise ceased when treatment with insulin was discontinued, although the glycosuria was unchanged.

The patient was seen at the Mayo Clinic in July 1946, and treatment with a mixture of protamine zinc insulin and regular insulin was begun. The glycosuria was not affected, but the malaise reappeared. The patient then was placed in the hospital for study. A number of studies designed to demonstrate the possible action of diphenhydramine hydrochloride in diminishing the resistance to the hypoglycemic effects of insulin were inconclusive. During one procedure, 100 units of crystalline insulin was injected intravenously, and within twenty minutes

TABLE 1.—*Direct Skin Tests with Crystalline Insulin in Case 1**

Solution Injected	Amount, Cc.	Maximal Size of Flare, Sq. Cm.
Isotonic solution of sodium chloride.....	0.2	0
Insulin U-40.....	0.2	16.0
Insulin, 1:10.....	0.2	14.5
Insulin, 1:100.....	0.2	13.9
Insulin, 1:5,000.....	0.2	7.2

* A similar series of tests performed in case 2 resulted in generalized urticaria within thirty minutes.

TABLE 2.—*Direct Skin Tests Before and Thirty Minutes After the Oral Administration of One Hundred Milligrams of Diphenhydramine Hydrochloride*

Solution Injected	Amount, Cc.	Maximal Size of Flare, Sq. Cm.		Reduction in Size of Flare, %
		Before Diphen- hydramine Hydro- chloride	After Diphen- hydramine Hydro- chloride	
Case 1				
Insulin U-40.....	0.2	10.3	9.8	4.8
Insulin, 1:10.....	0.2	17.6	9.8	44.3
Insulin, 1:50.....	0.2	14.5	6.2	57.2
Isotonic solution of sodium chloride.	0.2	0	0
Case 2				
Insulin, 1:5,000.....	0.2	14.5	2.0	86.2
Isotonic solution of sodium chloride.	0.2	0	0

generalized urticaria had developed. On the following day, when the intravenous injection of the same amount of insulin was preceded by the administration of 100 mg. of diphenhydramine hydrochloride orally, no allergic symptoms appeared. Direct skin tests were performed, in which a pronounced sensitivity to crystalline insulin was demonstrated (table 1). The oral administration of diphenhydramine hydrochloride moderately diminished the size of flares resulting from the intracutaneous injection of insulin (table 2). When the drug was mixed with the insulin prior to its intracutaneous injection, the size of the flares was reduced even more (table 3). Prausnitz-Küstner passive transfer tests proved the presence of circulating antibodies (reagins), and diphenhydramine hydrochloride was again found to modify the allergic reaction (table 4).

RESULTS OF TREATMENT WITH DIPHENHYDRAMINE HYDROCHLORIDE

In these 2 diabetic patients sensitive to insulin, maximal flaring was found to occur from five to thirty minutes after injection; the average time required for this maximal flaring to develop was fifteen minutes after the injection.

Neither the 0.9 per cent (isotonic) solution of sodium chloride nor the 1:1,000 dilution of diphenhydramine hydrochloride in 0.9 per cent solution of sodium chloride caused any flaring in any of the control subjects. The solution of diphenhydramine hydrochloride, however, frequently caused redness, confined to the mechanical wheal, which resulted from the intracutaneous injection of 0.2 cc.

In table 1 is shown the pronounced flaring produced by even high dilutions of insulin in case 1. When similar tests were carried out in case 2, generalized urticaria appeared within thirty minutes as a result of the injection of a total of 9 units of crystalline insulin intracutaneously.

In case 1 the size of the flare produced by undiluted U-40 insulin was diminished only 4.8 per cent, while the flares resulting from 1:10 and 1:50 dilutions were reduced 44.3 and 57.2 per cent respectively by the oral administration of 100 mg. of diphenhydramine hydrochloride. In the patient represented in case 2, who was extremely sensitive and who for this study, therefore, was given only the single injection of insulin in 1:5,000 dilution, the size of the flare was reduced 86.2 per cent (table 2). The dose of 100 mg. used in this procedure is somewhat larger than that ordinarily administered at one time but is within practical limits. The effect of such a dose reaches a maximum within thirty minutes and then gradually diminishes within the next three to six hours.²⁴

When diphenhydramine hydrochloride was mixed with the insulin, the allergic reaction was again modified (table 3). With oral administration of the former, flares were reduced in size from about 5 to 86 per cent, while the addition of the drug directly to the solution containing insulin caused reductions of from 75 to 100 per cent.

It seems clinically practical in instances of local allergic reactions to insulin to mix equal quantities (0.5 to 1.0 cc.) of a 1:1,000 solution of diphenhydramine hydrochloride with the daily dose of insulin.²² This proves to be advantageous in that only 0.5 to 1.0 mg. of diphenhydramine hydrochloride is required to achieve an effect comparable to that obtained by the oral administration of 50 to 100 mg. of the drug. Such a procedure thus eliminates the drowsiness and irritability experienced by some persons receiving the larger doses by mouth. In some persons, however, oral as well as parenteral administration of the drug

24. Leavitt, M. D.: A Study of the Action of Benadryl in the Skin of Human Beings, Thesis, Graduate School, University of Minnesota, 1946.

degree of sensitivity to insulin was imperative. Four units (0.1 cc.) of a commercial crystalline zinc insulin injected intradermally resulted in a large wheal, with a flare 6 cm. in diameter. Multiple areas of urticaria also were distributed over the body. Four units given subcutaneously caused slight induration, redness and tenderness. On the following day the patient received 150 mg. of diphenhydramine hydrochloride orally one hour before she was given 10 units (0.25 cc.) of crystalline zinc insulin intradermally. This second intradermal injection resulted only in a flare 2 cm. in diameter, and there were no general manifestations.

Cholecystectomy was performed. Postoperative treatment included the administration of 1 liter of a 10 per cent solution of dextrose intravenously on three occasions. To each liter was added 100 mg. of diphenhydramine hydrochloride; 30 units of crystalline insulin was administered subcutaneously at the beginning of

TABLE 4.—*Prausnitz-Küstner Passive Transfer Tests* *

Solutions Injected	Amount, Cc.		Maximal Size of Flare, Sq. Cm.		Reduction in Size of Flare, %	
Case 1						
Insulin 1:10.....	0.1	}	32.0	}	58.8	
Isotonic solution of sodium chloride.....	0.1					
Insulin 1:10.....	0.1	}	13.4	}		
Diphenhydramine hydrochloride 1:1,000.....	0.1					
Insulin 1:50.....	0.1	}	20.6	}	69.9	
Isotonic solution of sodium chloride.....	0.1					
Insulin 1:50.....	0.1	}	6.2	}		
Diphenhydramine hydrochloride 1:1,000.....	0.1					
Case 2						
Insulin 1:100.....	0.1	}	13.9	}	89.2	
Isotonic solution of sodium chloride.....	0.1					
Insulin 1:100.....	0.1	}	1.5	}		
Diphenhydramine hydrochloride 1:1,000.....	0.1					
Insulin 1:5,000.....	0.1	}	7.2	}	57.0	
Isotonic solution of sodium chloride.....	0.1					
Insulin 1:5,000.....	0.1	}	3.1	}		
Diphenhydramine hydrochloride 1:1,000.....	0.1					

* The same solutions injected into the unprepared skin of a normal subject caused no erythema.

each infusion. There was slight induration at each site, but no redness or pruritus. No generalized reaction occurred. Ten days later an elective anterior colporrhaphy was done. Postoperative treatment included the administration of 1 liter of a 5 per cent solution of dextrose intravenously on two occasions. Ten units of crystalline insulin was given subcutaneously with each infusion. Diphenhydramine hydrochloride was not given with either of these injections, and an area of slight redness and induration, 2 to 4 cm. in diameter, resulted. Glycosuria was then controlled by diet alone.

The patient returned in August 1946 for dental extractions. Direct skin tests and Prausnitz-Küstner passive transfer tests were performed at this time. The results are reported in tables 2, 3 and 4. The results of these two procedures were similar to those obtained in case 1, although the degree of sensitivity in case 2 was higher.

Editorial

SUDDEN DEATHS IN THE ARMY

MORITZ and Zamcheck¹ present an interesting survey of the material for autopsy at the Army Institute of Pathology concerning 1,000 sudden deaths from disease of apparently healthy soldiers between 18 and 40 years of age. The most common diseases responsible for rapid, unexpected death among young soldiers were cardiac disease, intracranial hemorrhage and meningococcemia. There were 350 sudden deaths from previously unrecognized cardiac disease, of which about 300 were due to coronary arteriosclerosis. Eight per cent of this group were under 25 years of age, and 22 per cent were younger than 30. White and Negro soldiers were represented in proportion to their numbers in the army. The frequency with which the onset of the fatal attack of coronary insufficiency occurred during a period of strenuous physical exertion lends support to the opinion that violent exercise is dangerous for persons suffering from severe coronary disease. However, this information is not of great practical value to the Army in the prevention of such casualties, because none of the soldiers was suspected of having cardiac disease prior to death and fewer than 25 per cent of them had a history of symptoms suggesting cardiac origin. The authors, therefore, express the opinion that the practicability of conducting complete cardiologic studies on all soldiers who admit having occasional twinges of abdominal or epigastric discomfort is of questionable value. The autopsies in these cases disclosed in all instances severe atherosclerosis of one or both coronary arteries. Thrombotic occlusion was recognized in about 25 per cent, and it was apparent that in most of these the fatal thrombus had begun to form some hours or days before it became symptomatic.

In 69 of 91 reviewed cases of sudden death from nontraumatic intracranial hemorrhage, the bleeding was principally subarachnoid and was either proved or inferred to have resulted from the rupture of a superficial aneurysm of the congenital or berry type. There was some indication that aneurysms of this type are more likely to rupture during a period of violent physical exertion than during sleep. About 20 per cent of these soldiers gave a history of headaches. At autopsy the bleeding was found to be confined to the subarachnoid space in about 65 per cent and was both parenchymatous and subarachnoid in 35 per cent. In 110, or approximately one third of all reported cases of death

1. Moritz, A. R., and Zamcheck, N.: Sudden and Unexpected Deaths of Young Soldiers, *Arch. Path.* **42**:459 (Nov.) 1946.

may be required to control local symptoms. Control of generalized manifestations of insulin allergy most likely will require oral administration of diphenhydramine hydrochloride in addition to that injected with the insulin.

Circulating antibodies (reagins) were demonstrated in the serums of both patients by the Prausnitz-Küstner passive transfer test. This test was performed by injecting 0.2 cc. of the patient's serum intradermally into a nonallergic subject at various sites. Twenty-four hours later, 0.2 cc. of the various dilutions of insulin with and without diphenhydramine hydrochloride were introduced intradermally at the prepared sites. Simultaneous control tests on the unprepared skin of the same subject caused no flaring. When a 1:1,000 solution of diphenhydramine hydrochloride was mixed with the antigen (insulin), the size of flares in the 2 cases was reduced from 57.0 to 89.2 per cent as compared with flares produced by the injection of various dilutions of insulin without the addition of the drug in the prepared sites. Thus it is seen that the reaction between the antigen and the circulating antibodies may be modified by the use of diphenhydramine hydrochloride.

SUMMARY AND COMMENT

Two cases in which allergy to insulin characterized by generalized urticaria was exhibited have been reported.

Studies conducted reveal that in these 2 cases diphenhydramine hydrochloride favorably modified the dermal symptoms of the allergic state and afforded a satisfactory method for treating such symptoms.

In the light of these results, it would seem desirable to have a solution of diphenhydramine hydrochloride available for parenteral administration. Such a solution might be effective in the treatment of localized allergic reactions to a number of injected substances, such as liver extract, hormones, drugs and serums as well as insulin.

Correspondence

EOSINOPHILIC GRANULOMA OF BONE SYNONYMOUS WITH SCHÜLLER-CHRISTIAN DISEASE, LIPID GRANULOMA, ESSENTIAL XANTHOMATOSIS OF NORMOCHOLESTEREMIC TYPE AND EOSINOPHILIC XANTHOMATOUS GRANULOMA

To the Editor:—The reader of the article "Eosinophilic Granuloma of Bone: Report of a Case with Multiple Lesions of Bone and Pulmonary Infiltration", by A. Weinstein, H. C. Francis and B. F. Sprockin, published in this journal (79:176 [Feb.] 1947) may become confused on the issue of whether "eosinophilic granuloma of the bone" is a newly discovered disease entity or whether it is a part of a systemic disorder formerly described under different designations such as "Schüller-Christian disease" (Rowland, 1928), "lipid granulomatosis" (by Chester, 1930, and Fraser, 1934) and "essential xanthomatosis of the normocholesteremic type" (Thannhauser and Magendanz, 1937). The following presentation illustrating historically the conception of the pathogenesis of the disease may contribute toward the clarification of some misunderstanding concerning its classification.

Schüller described in 1915¹ "peculiar defects of the membranous bones of the skull," referring later, in 1921,² to "a peculiar syndrome of dyspituitarism." Christian in 1919³ called attention to a clinical syndrome consisting in "defects in membranous bones, exophthalmos and diabetes insipidus." Hand⁴ had already observed a case which belonged in this group, in 1893, but classified the condition as "polyuria and tuberculosis." After the syndrome had been clinically established, the pathologist Rowland in 1929⁵ demonstrated that the histologic lesions characteristic of Schüller-Christian syndrome consist of reticulum cells and histiocytes, cholesterol-containing foam cells and elements of acute inflammation, like eosinophils, round cells and polynuclear elements. Rowland considered the development of foam cells as characteristic of the lesion, as had been previously suggested by the dermatologists Weidman and Freeman in 1924⁶ on the basis of two autopsies on patients with lesions of the skin, central nervous system and other organs. In his pioneer work on the histologic changes in Schüller-Christian syndrome Rowland had already described the occasional involvement of the lung and supplemented the description of the pathologic process in the lung with characteristic roentgenograms,

1. Schüller, A.: Ueber eigenartige Schädeldefekte im Jugendalter, Fortschr. a. d. Geb. d. Röntgenstrahlen **23**:12, 1915-1916.

2. Schüller, A.: Ueber ein eigenartiges Syndrom von Dyspituitarismus, Wien. med. Wchnschr. **71**:510, 1921.

3. Christian, H. A.: Defects in Membranous Bones, Exophthalmos and Diabetes Insipidus, in Contributions to Medical and Biological Research, New York, Paul B. Hoeber, 1919, vol. 1, p. 390; M. Clin. North America **3**:849, 1920.

4. Hand, A.: Polyuria and Tuberculosis, Arch. Pediat. **10**:673, 1893.

5. Rowland, R. S.: Xanthomatosis and the Reticulo-Endothelial System, Arch. Int. Med. **42**:611 (Nov.) 1928; Ann. Int. Med. **2**:1277, 1929.

6. Weidman, F. D., and Freeman, W.: Xanthoma Tuberosum: Two Necropsies Dislosing Lesions of Central Nervous System and Other Tissues, Arch. Dermat. & Syph. **9**:149 (Feb.) 1924.

from meningococcic infections, death occurred within twenty-four hours after the onset of incapacitating symptoms. The incidence was higher in Negroes than in white troops. More than half of the patients in this group died within six hours after coming under medical observation. In approximately 70 per cent of the cases the soldier was reported to have been below par or to have been suffering from a mild infection of the upper respiratory tract prior to the onset of the fulminating phase of the disease. This suggests that a "cold" or minor indisposition complained of by a soldier who may have been exposed to persons with meningococcic infections should not be ignored. The majority of the patients were characterized clinically as suffering from the Waterhouse-Friederichsen syndrome, some with and many without evidence of meningeal invasion. At autopsy, purpura or cutaneous petechiae were recognized in 80 per cent of these men. Focal or massive adrenal hemorrhages were encountered in 71 per cent. In most of the hemorrhagic and nonhemorrhagic adrenal glands, microscopic examination of the cortex disclosed degeneration and necrosis of the tubular type. Adrenal apoplexy occurred in some cases without cutaneous hemorrhages, and again cutaneous purpura was encountered without hemorrhage of the adrenal glands. The impression was gained that adrenal hemorrhage in fulminating meningococcemia was usually preceded by degenerative changes in the cells of the glomerular and fascicular zones of the cortex. Medullary damage was characteristically absent, minimal or terminal.

In addition to the foregoing, there were at least 140 carefully investigated sudden deaths in which the findings at autopsy were essentially normal. They represented more than 10 per cent of all sudden non-traumatic deaths of apparently healthy young men. The racial and age distribution of the soldiers dying of obscure causes corresponded to those of the army as a whole, and weights did not differ from those of soldiers dead of accidental violence or of acute infections. There was no apparent relationship between the onset of the fatal seizure and what the soldier was doing at the time of the attack. Thus, the number of seizures that occurred during sleep or during strenuous exertion was roughly proportional to the number of hours that the average soldier devoted to such activities.

The authors conclude that the methods of examination available to the pathologist are frequently inadequate to disclose either the extent or the nature of certain disorders even though they are of sufficient severity to be incompatible with life.

not only to solitary lesions of the bone but also to those of "Schüller-Christian syndrome" as well as to the generalized lesions in other organs in the group of diseases formerly classified as "lipid granulomatosis" or clinically designated as "essential xanthomatosis of the normocholesteremic type." Through the histologic studies of Teilum and his co-workers it was demonstrated that the natural history of such an "eosinophilic granuloma" comprised the following phases: (1) a proliferative phase, in which histiocytic proliferation associated with accumulation of eosinophilic leukocytes is observed (see also article by Fraser); in this phase there is no evidence of foam cells; (2) a granulomatous phase, with increase of blood vessels and fibrils, reticular cells and histiocytes, eosinophils and giant cells (Touton cells) and incipient lipid phagocytosis; (3) a xanthomatous phase, with nests and isolated foam cells, and (4) a fibrous stage, considered as a healing phase. These four phases often show no strict demarcation during the course of the disease, and the histologic features of the stages may overlap considerably during the course of the disease. It is evident from the histologic studies of Teilum as well as of Farber that solitary "eosinophilic granuloma" is the monosymptomatic early stage of a systemic disease designated by Chester as well as by Fraser as "lipoid granulomatosis," by Rowland as "Schüller-Christian syndrome" and by Thannhauser and Magendantz, from the clinical point of view, as "essential xanthomatosis of the normocholesteremic type."

The paper of Jaffe and Lichtenstein has caused considerable misunderstanding about the classification of the disease under discussion, as is seen in recent publications cited in the article of Weinstein and his co-workers. The earlier authors as well as Lichtenstein and Jaffe refer to the same disease. The designation of the disease under discussion as "eosinophilic granuloma" is incomplete and therefore misleading, since "eosinophilic granuloma" is not a disease entity but only a phase in the histologic aspect of a distinct clinical syndrome. The formation of xanthoma cells in the later phases of the lesions is as characteristic of the disease as the reticulohistiocytic proliferation and the accumulation of eosinophils in its earlier phases. If one does not prefer to use the older names "Schüller-Christian syndrome," "lipoid granulomatosis" or "normocholesteremic xanthomatosis," one should think of a classification which at least refers to the two outstanding histologic phases of the granuloma, namely, the proliferative and eosinophilic phase and the xanthomatous phase. The designation of the localized and systemic disorder as "eosinophilic xanthomatous granuloma" seems to be more appropriate, even if it does not embrace the reticulohistiocytic proliferation of the early lesion. Such a name would also prevent further misunderstanding in the conception and classification of this disorder.

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PENICILLIN IN TREATMENT OF KERATOSIS BLENNORRHAGICA

To the Editor:—My attention was recently called to an article which appeared in the ARCHIVES by Freireich, Schwartz and Steinbrocker—"Penicillin in the Treatment of Keratosis Bleennorrhagica with Polyarthrits" (79:239-250 [Feb.] 1947).

In this paper the authors state that "no record of therapy for keratosis bleennorrhagica with penicillin has appeared in the literature." May I respectfully call

as others did later. Chester in 1930⁷ demonstrated the granulomatous nature of the lesions and classified the disease as "lipid granuloma." The most complete histologic description of solitary lesions of the bone, supported by excellent histologic pictures in color, are found in the paper "Skeletal Lipoid Granulomatosis" by Fraser in 1935. Fraser⁸ had already called attention to the endothelial proliferation, the accumulation of eosinophilic cells and the presence of giant cells in the earlier stages of the lesion in "lipoid granuloma." Thannhauser and Magendantz in 1937⁹ demonstrated, on the basis of numerous clinical observations of cases of xanthomatous diseases of heterogeneous origin, that in cases of Schüller-Christian syndrome and those of generalized lipid granulomatosis there was normal cholesterol content of the serum in contrast to that in other groups of xanthomatous disease with hypercholesteremia. For this reason they used the name "essential xanthomatosis of the normocholesteremic type" for Schüller-Christian syndrome and the generalized form of "lipoid granulomatosis." The cholesterol content of the tissues in this disorder in its xanthomatous phase is ten to twenty times higher than that in normal tissue, while the cholesterol level of the serum remains normal. These authors, therefore, contended that the accumulation of cholesterol in the xanthomatous cells in this disorder is not the result of infiltration of cholesterol from the blood stream but is caused by new formation of cholesterol within those cells which gradually develop into xanthoma cells (foam cells). Thannhauser and Magendantz showed in their clinical material and in the cases reported in the literature that various organs (skin ["disseminata" type of xanthoma], osseous system, dura, brain, lung, pleura, liver, spleen and lymph nodes) may be involved singly or in various combinations in the systemic disease under discussion.

Lichtenstein and Jaffe reported in 1940¹⁰ in a histologic study, cases of solitary lesions of the bone, which they designated as "eosinophilic granuloma of bones." They apparently believed at the time that this type of solitary granuloma of the bone was a disease not hitherto described. They were evidently not familiar with the exhaustive histologic description by Fraser in 1934 of several cases of such disease ("skeletal lipoid granulomatosis") or with case 20 in the article on "Different Clinical Groups of Xanthomatous Diseases" by Thannhauser and Magendantz.

It was not until the studies of Farber and his co-workers¹¹ and of Holm, Teilum and Christensen¹² that the designation "eosinophilic granuloma" was applied

7. Chester, W.: Ueber Lipoidgranulomatose, *Virchows Arch. f. path. Anat.* **279**:561, 1930.

8. Fraser, J.: Lipoid Granulomatosis of the Bones, *Brit. J. Surg.* **22**:800, 1935.

9. Thannhauser, S. J., and Magendantz, H.: The Different Clinical Groups of Xanthomatous Diseases: A Clinical Physiological Study of Twenty-Two Cases, *Ann. Int. Med.* **11**:1662, 1938. Thannhauser, S. J.: *Lipidoses*, New York, Oxford University Press, 1940.

10. Lichtenstein, L., and Jaffe, H. L.: Eosinophilic Granuloma of Bone, with Report of a Case, *Am. J. Path.* **16**:595, 1940.

11. Green, W. T., and Farber, S.: "Eosinophilic or Solitary Granuloma" of Bone, *J. Bone & Joint Surg.* **24**:499, 1942. Farber, S.: The Nature of "Solitary Eosinophilic Granuloma" of Bone, *Am. J. Path.* **17**:625, 1941; The Nature of Some Diseases Ascribed to Disorders of Lipid Metabolism, *Am. J. Dis. Child.* **68**:350 (Nov.) 1944.

12. Holm, J. E.; Teilum, G., and Christensen, E.: Eosinophilic Granuloma of Bone: Schüller-Christian's Disease, *Acta med. Scandinav.* **118**:292, 1944.

News and Comment

GENERAL NEWS

Conference on Antihistamine Agents in Allergy.—A conference on antihistamine agents in allergy will be held on Oct. 3 and 4, 1947, under the auspices of the New York Academy of Sciences. The program follows:

FRIDAY MORNING, OCTOBER 3, 9:30 A. M.—12:30 P. M.

Chairman: DR. FREDRICK F. YONKMAN

"The Pharmacodynamics of Histamine," Sir Henry H. Dale, formerly Director of the National Institute for Medical Research, Mount Vernon House, N. W. 3, England

"The Role of Histamine and Other Metabolites in Anaphylaxis," Dr. Carl A. Dragstedt, Professor of Pharmacology, Northwestern University Medical School, Chicago

"The Role of Blood Platelets and Leukocytes in Anaphylaxis," Dr. M. Rocha e Silva, Professor of Pharmacology and Biochemistry, Instituto Biologica, Sao Paulo, Brazil

FRIDAY AFTERNOON, OCTOBER 3, 2:00 P. M.—5:00 P. M.

Chairman: DR. ROBERT COOKE

"The Immunologic Aspects of Anaphylaxis and Allergy," Dr. M. W. Chase, Rockefeller Institute, New York

"The Detoxification of Histamine," Dr. E. T. Waters, Banting and Best Department of Medical Research and Department of Physiology, University of Toronto, Toronto, Canada

"Histamine-Azo-Proteins in Anaphylaxis and Allergy," Dr. N. Fell, Camp Detrick, Frederick, Md.

SATURDAY MORNING, OCTOBER 4, 9:30 A. M.—12:30 P. M.

Chairman: DR. GEORGE RIEVESCHL JR.

"Introduction to Antihistamine Agents and Antergan Derivatives," Dr. D. Bovet, Professor of Pharmacology, University of Rome, Italy

"The Activity of Pyribenzamine and Related Compounds with Special Reference to Their Mode of Action," Dr. Rudolf L. Mayer, Division of Research, Ciba Pharmaceutical Products, Inc., Summit, N. J.

"The Pharmacology of Benadryl and the Specificity of Antihistamine Drugs," Dr. Earl R. Loew, Department of Pharmacology, University of Illinois College of Medicine, Chicago

SATURDAY AFTERNOON, OCTOBER 4, 2:00 P. M.—5:00 P. M.

Chairman: DR. SANFORD B. HOOKER

"Antistine and Related Imidazolines," Dr. Rolf Meier, Medical Director, Ciba Limited, Basel, Switzerland, and Professor of Pharmacology and Therapeutics, University of Basel, Switzerland

"The Mechanism of Action of Antihistamine Agents with Special Reference to Their Mode of Action in the Skin," Dr. Charles F. Code, The Mayo Foundation, Rochester, Minn.

your attention to my article, "Keratoderma Blennorrhagicum: Brief Review and Report of a Case Treated with Penicillin," which appeared in the *American Journal of Syphilis, Gonorrhea and Venereal Diseases* (29:361-371 [May] 1945)?

E. M. SATULSKY, M.D., Elizabeth, N. J.

To the Editor:—There is no doubt that Dr. Satulsky can claim priority in the use of penicillin in keratosis blennorrhagica. However, in all fairness, one should quote the entire sentence from our article, which reads, "To our knowledge, no record of this type of therapy for keratosis blennorrhagica has appeared so far in the literature." Unfortunately, Dr. Satulsky's article escaped our attention when our work was submitted. When the first draft of our paper was prepared, his article had not yet been published. The patient in our case 1 was started on medication with penicillin on Oct. 14, 1944, and the patient in case 2 received it on Oct. 2, 1944, approximately seven months before the appearance of his article in the literature. Although there is no question that his patient, who received his first dose of penicillin on Jan. 24, 1944, obtained this type of therapy before our patients did, it was without any knowledge of his work that we instituted similar treatment.

A. W. FREIREICH, M.D., Malverne, N. Y.

Book Reviews

Clinical Electrocardiography. By David Scherf, M.D., and Linn J. Boyd, M.D. Second edition. Price, \$8. Pp. 267, with 243 illustrations. Philadelphia: J. B. Lippincott Company, 1946.

The second edition of this excellent treatise on electrocardiography has been revised and reset in a two column format. This change only partly overcomes a common and trying minor annoyance to one studying books of this kind carefully, namely, that the discussion of a tracing often follows a page or two behind its occurrence in the book.

As the authors mention in their preface, more and more physicians, with the ready availability of recording devices, are dabbling in electrocardiography, and unwarranted ideas about the simplicity of interpretation are widespread, the limitations and uncertainties of the method being inadequately stressed. This misconception is carefully emphasized, and another fault of many textbooks, i. e., the tacit assumption that certain basic useful working hypotheses have been established as fact, is avoided. Adherence to these principles produces a book which neophytes will find confusing and difficult but which will reward them richly for careful study and which is invaluable to the mature student.

The generally superb quality of the discussions is seriously marred by the fact that chest leads are considered separately in a single chapter and then the discussion is largely confined to CR₂ and CR₄. Indeed, in the whole chapter on myocardial infarction only one chest lead is reproduced, and none is shown in the chapter on the exercise tolerance test in coronary sclerosis. The freedom with which the authors use as equivalents the terms "myocardial infarction" and "coronary thrombosis" is regrettable.

The chapters on pericarditis, pulmonary embolism and changes associated with endocrinopathies are required reading for all who interpret electrocardiograms, and the lengthy sections on the arrhythmias are the best available source of thoughtful and objective information on this subject. Interference dissociation, reciprocal rhythm, parasystole and the concept of exit blockade are discussed in detail.

Despite the minor criticisms mentioned, this book adequately presents a summary of the practical aspects of electrocardiography and provides excellent correlation of electrocardiographic with clinical findings.

Principles of Dynamic Psychiatry. Including an Integrative Approach to Abnormal and Clinical Psychology, with a Glossary of Psychiatric Terms. By Jules H. Masserman. Price, \$4. Pp. 322, with 4 illustrations. Philadelphia: W. B. Saunders Company, 1946.

There is a growing tendency for psychiatry and internal medicine to grow closer. Older clinicians say that this is not a new idea; younger ones, however, are inclined to talk of psychosomatic medicine and seem to feel that instead of caring for ill patients with the help of insight and sympathy, as Francis Peabody suggested, they can accomplish better results by more elaborate psychiatric methods. A book such as this is extremely helpful. It presents in clear and readable form the ideas of a psychiatrist who has worked in the field of internal medicine; it describes the manner in which the complex problems of thought are being approached by experts, and it outlines current knowledge of the methods of measuring behavior. The book also has two other valuable features. The first is its glossary; here, as the author says, the internist can find the meaning of about twelve hundred of the more obscure terms found in current psychiatric literature, thus learning to translate into his own vernacular articles or books which, though printed in English, often seem unduly hard to comprehend. The second is an admirable bibliography and index.

"Antihistamine Therapy, Experimental and Clinical Correlation," Dr. Samuel M. Feinberg, Department of Allergy, Northwestern University Medical School, Chicago

Requests for further information and inquiries about attending the conference should be addressed to the executive secretary of the Academy, Eunice Thomas Miner, Central Park West at Seventy-Ninth Street, New York 24.

Poliomyelitis Conference Set for Georgia Warm Springs September 15, 16 and 17.—Marking the twentieth anniversary of the founding of Georgia Warm Springs, a three day clinical conference on diagnosis and treatment of poliomyelitis will be held at Warm Springs, Ga., on September 15, 16 and 17.

The clinical conference will be led by approximately twenty of the nation's authorities in the fields of neurology, pathology, pediatrics, orthopedics, physical medicine and internal medicine, who will present papers reviewing the advances in the knowledge of poliomyelitis in these fields.

The papers and discussions will constitute the material for a new book on diagnosis and treatment of the disease for publication in 1948. Clinical demonstrations of modern methods of treatment will be given by the medical staff of the Warm Springs Foundation.

Physicians interested in attending this conference should send inquiries to the Georgia Warm Springs Foundation, 120 Broadway, New York 5, N. Y. A complete program of the meeting will be available on request.

Sixth International Short Wave Congress.—The Sixth International Short Wave Congress will be held in Amsterdam, Netherlands, July 19 to 24, 1948. Those who wish to take part in the congress are requested to communicate with Dr. J. Samuels, Weteringschans 73, Amsterdam, Netherlands. Manuscripts should be sent before April 15 at the latest to W. F. K. Gouwe, Lutten-Dedemsvaart, Netherlands.

Graduate Fortnight, New York Academy of Medicine.—A graduate fortnight will be held again this year at The New York Academy of Medicine, October 6 to 17, inclusive. It will be devoted to the study of disorders of metabolism and the endocrine glands.

An especially valuable and time-saving addition to the usual bibliography is the concise abstract appended to the majority of the references. These are well written and give the essential facts of the article, so that any worker can quickly determine whether the entire paper should be read. Also many of these abstracts are from journals not readily available or from articles in foreign languages not understood by many. The wealth of detailed material in these abstracts is surprising, and one gains the impression that the pith of the paper is presented.

The breadth of this stupendous work can be partially understood by the range of the languages translated. In addition to the American and English publications, which are particularly rich in clinical and virus research work on infantile paralysis, the following languages are covered: Danish, French, German, Hungarian and other Slavic languages, Icelandic, Italian, Japanese, Norwegian, Portuguese, Spanish, Swedish and Russian.

The complete author and subject indexes will prove invaluable to everyone working on infantile paralysis. Thanks to the system of numbering all references, all the articles published between 1789 and 1945 by any individual author or on any particular phase of the subject can be instantly determined. The subject index is exceedingly complete, with alphabetically arranged subheadings following the list of numbers of all references covering the particular subject. For example, under the heading "contagiousness" there are thirty-eight subheadings, each with the numbers of the references covering this particular phase of the subject. The main headings are in bold type, and all annotations are in type sufficiently large to make for easy reading.

Such a monumental work would not have been undertaken and could not have been brought to a successful conclusion without the financial support of a great foundation. It seems fitting that this outstanding publication was made possible by the National Foundation for Infantile Paralysis. Great credit is due the administration of this foundation, particularly its president, Basil O'Connor, for conceiving the need for such a work and wholeheartedly backing its production. The reviewer also wishes to commend particularly the editor, Morris Fishbein, whose guiding interest and enthusiastic cooperation insured its successful and early completion. The vital roles played by Ludvig Hektoen and Ella Salmonsens can best be judged by perusing the work.

It is proposed to issue a supplementary volume every two years and at the end of ten years to compile these into a second single volume bibliography.

This bibliography of infantile paralysis with selected abstracts and annotations can well serve as the model for all future bibliographies on any medical subject. It should be in the library of everyone concerned in clinical or laboratory investigations of poliomyelitis.

Howell's Textbook of Physiology. Edited by John F. Fulton, M.D., with the collaboration of Donald H. Baron and others. Fifteenth edition. Price, \$8. Pp. 1,304, with 507 illustrations. Philadelphia: W. B. Saunders Company, 1946.

In preparing the fifteenth edition of this classic American text, the editor has enlisted the collaboration of a group of associate editors, each responsible for one of the ten sections of the book. Each of them has secured various contributors for different portions of the text. In a field such as physiology, in which additional factual knowledge is being accumulated so rapidly and in which viewpoints, of necessity, must change, it is a difficult or impossible task for one person to present a picture in clear perspective. In his organization of the task before him, Dr. Fulton has succeeded in carrying out Dr. Howell's guiding principle as stated in the previous edition—"First, the importance of simplicity and lucidity in the presentation of facts and theories, and, second, the need of a judicious limitation of the material selected." Both objectives have been attained in the preparation of a ready reference text for students and practitioners. In spite of a large amount of rewriting necessary because of the date and new points of view, Dr. Fulton has succeeded in carrying out Dr. Howell's objective and in continuing the book as the leading American text, indispensable to every physician's library.

On the whole, the work deserves high praise. Medical students and teachers are certain to find it a useful tool, while ordinary readers can learn a great deal from it.

Electrocardiography. By Louis N. Katz, M.D. Second edition. Price, \$12. Pp. 883, with 525 illustrations. Philadelphia: Lea & Febiger, 1946.

The ARCHIVES (69:368 [Feb.] 1942) reviewed the first edition of this book in a complimentary manner. It seemed a scholarly work and was handsomely printed and profusely illustrated. The only possible complaint—and this was minor—concerned the author's meticulousness; parts of the book made rather heavy reading because of his zealous attention to detail.

The second edition is a revision of the first; it is 203 pages longer, containing more than a hundred additional illustrations and selling at an increased cost of \$2. It continues to be an admirable text, so that all the pleasant things said of the first edition can be repeated. It is certain to achieve great popularity.

A Bibliography of Infantile Paralysis, 1789-1944, with Selected Abstracts and Annotations. Prepared under Direction of the National Foundation for Infantile Paralysis, Inc. Edited by Morris Fishbein, M. D., Editor, Journal of the American Medical Association. Compiled by Ludvig Hektoen, M.D., Chief Editor, Archives of Pathology, and Ella M. Salmonsens, Medical Reference Librarian, John Crerar Library, Chicago. Cloth. Price, \$15. Pp. 672. Philadelphia: J. B. Lippincott Company, 1946.

This is without question the finest bibliography on any subject ever published. Probably no bibliography has ever been as completely and carefully compiled. Every reference has been checked and rechecked with the original article. The periodical literature of the world has been examined and the references to all important clinical and investigative work on infantile paralysis recorded. The volume starts with the first definite descriptions of the disease by Underwood in 1789 and ends with references to articles published in December 1944.

The book is beautifully printed on excellent paper in large clear type. If the term artistic can be applied to a bibliography, this work certainly merits such a designation. The page is of convenient size and arrangement for easy reading, and the volume, in spite of the 672 pages, is light and readily handled.

Over 8,750 references to infantile paralysis are included. These are largely from periodical literature, as is proper. The material in textbooks, systems of medicine and encyclopedias is rarely new and is generally a compilation from more detailed articles in the current literature; hence little or no attention was devoted to such sources and to the more general discussions of poliomyelitis found in publications of boards of health and in those on general health education.

This bibliography has a unique arrangement, the references being first listed under the year of publication. It is interesting to note the gradual increase in the number of titles from 1789, when the first references appeared, to the beginning of the twentieth century. From then on the greatly augmented publication of medical journals and the increasing interest in poliomyelitis sharply accentuate the number of pertinent articles. The arrangement of references by years allows a reader to ascertain readily what progress has been made at any period and to determine whether certain articles would be of purely historical value and what papers, especially those dealing with research, may be considered of immediate importance.

Under the respective yearly headings, the titles are arranged alphabetically according to authors, each being numbered for facility in location in both the author and subject index. The number and author's name are printed in bold type, making quick reference possible. The complete title in the original language follows, with translation into English when other than English was used. The name of the publication and the volume, page and date are given in the form approved by *The Journal of the American Medical Association*.



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SARCOIDOSIS

A Clinical and Roentgenologic Study of Twenty-Eight Proved Cases

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WHILE serving in an army general hospital which functioned as a center for radiation therapy, we were afforded an opportunity to study a large number of mediastinal tumors. A clinical and histologic diagnosis of sarcoidosis was established in 28 cases. It was thought worth while to assemble this group of cases and assess the values of the clinical and roentgenologic features of the disease. The most pressing problem in the diagnosis of a mediastinal tumor is the differentiation of benign from malignant lymphogranuloma. The factors bearing on this differential diagnosis are presented.

Since Besnier¹ described *lupus pernio* in 1889 and Boeck² ten years later studied the histologic structure in his cases of "multiple benign sarcoid of the skin," dermatologists have become increasingly aware of the cutaneous features of the disease. It was not until Schaumann³ in 1914 first realized that the cutaneous lesions described by Besnier and Boeck were in reality only a part of a generalized disease with characteristic pathologic changes in various internal organs that the present sound concept of the disease was possible. Jüngling's⁴

1. Besnier, E.: *Lupus pernio de la face; synovites fongueuses (scrofulotuberculeuses); symétriques des extrémités*, Ann. de dermat. et syph. **10**:333-336, 1889.

2. Boeck, C.: *Multiple Benign Sarcoid of the Skin*, J. Cutan. & Genito-Urin. Dis. **17**:543-555, 1899.

3. Schaumann, J.: *Lymphogranulomatosis Benigna in the Light of Prolonged Clinical Observations and Autopsy Findings*, Brit. J. Dermat. **48**:399-410, 1936.

4. Jüngling, O.: *Ueber Ostitis tuberculosa multiplex cystoides, zugleich ein Beitrag sur Lehre von den Tuberkuliden des Knochens*, Beitr. z. klin. Chir. **143**:401-475, 1928.

Exercises in Electrocardiographic Interpretation. By Louis N. Katz, M.D. Second edition. Price, \$6. Pp. 288, with 141 illustrations. Philadelphia: Lea & Febiger, 1946.

The ARCHIVES (69:160 [Jan.] 1942) reviewed the first edition of this book, characterizing it as an outcropping of a tendency toward reviving, in a new field, Dr. Richard C. Cabot's plan of "case teaching in medicine" by the study of paper patients. The volume described how to interpret electrocardiograms and then presented a series of case reports, each accompanied with beautifully reproduced electrocardiographic tracings pertinent to the cases described and intelligently and skilfully interpreted. The prediction was made that such a method of teaching electrocardiographic interpretation might prove helpful to many groups of physicians and students.

This prophesy has been fulfilled. As the author says, the reception of the first edition demonstrated that it helped to fill a significant need. He now has revised it, making certain changes in the cases reported and editing his work thoroughly. Thus the second edition follows the general plan of the first, is more up-to-date and is an improved model. He hopes that it will be as useful as its predecessor. It promises to be even more popular.

Roentgen Diagnosis of Diseases of the Gastrointestinal Tract. By John T. Farrell Jr., M.D. Price, \$5.50. Pp. 271, with 193 illustrations. Springfield, Ill.: Charles C Thomas, Publisher, 1946.

This is an interesting text, dealing with its subject in an orderly and precise manner. One of its most original features is its typography. While disorders of the gastrointestinal tract are listed with due orthodoxy, those which are usually detected by roentgenologists, those which are discussed in this text and those which are illustrated are listed in bold-faced type; those which are discussed but not illustrated are listed in light-faced type, and those which can be detected roentgenologically but which are neither discussed nor illustrated are listed in italics. The nomenclature used is that outlined in "Standard Nomenclature of Disease" and approved by the American Medical Association.

Once a reader familiarizes himself with these features, he finds the book readable and easy to follow. There are many illustrations which reproduce roentgenograms with unusual clarity. The descriptive writing is well done, clearly by a teacher who knows how to express his ideas forcibly and succinctly. Without doubt this is a useful volume, promising to be popular with radiologists, clinicians and students.

Allergy. By Erich Urbach, M.D., and Philip M. Gottlieb, M.D. Second edition. Price, \$12. Pp. 968, with 410 illustrations. New York: Grune & Stratton, Inc., 1946.

The ARCHIVES reviewed the first edition of this book (72:427 [Sept.] 1943). There were a few minor criticisms, chiefly the authors' coinage of words. They manufactured tongue twisters like "allergic pathergy," "parallurgy" and "allergization" instead of using more understandable expressions. Also they devoted considerable space to "propepton" therapy, which not all American allergists had accepted. On the whole, however, the review was complimentary, praising the book's thoroughness and the manner in which its subject matter was arranged and mentioning almost with awe its mammoth size.

Clearly, it has had a successful career, for now the second edition is at hand. This continues to be a large and handsome affair, discussing in detail almost every phase of its title. The authors still use new words which are a trifle difficult for an older internist to comprehend. "Propepton" continues to receive considerable attention. A double column format has been adopted to prevent overbulkiness.

The bibliography has been brought up-to-date and appears to be complete. The second edition promises to achieve the same degree of popularity as did its predecessor. Certainly it is a commendable text.

of sarcoid were found therein (case 27). There are few reports of sarcoid in the tonsils in the American literature. The failure to observe tonsillar involvement in this country as compared with the Scandinavian countries may be the result of the much more frequent performance of tonsillectomy in childhood here.

Cerebral manifestations of sarcoid have been known to occur. Roos¹³ collected 8 cases of "lymphogranulomatosis benigna" in which there were neurologic signs. In 3 fatal cases which were studied histologically there were basal lesions; in 2 these were located in the brain and in the other in the meninges. Most of the other patients showed signs indicating a basal location of the lesion, and 2 had diabetes insipidus. Kraus¹⁴ reported the autopsy observations in an instance of sarcoidosis with clinical diabetes insipidus.

In 6 autopsies Nickerson¹⁵ found sarcoid lesions in the spleen in 6 instances and in the lungs in 4. Unusual localizations were found in the myocardium, endocardium, pancreas, testis and vertebral and femoral bone marrow. Chronic interstitial myocarditis was found in 2 of 4 cases studied pathologically by Schaumann,³ while Longcope and Fisher¹⁶ found sarcoidosis in both the myocardium and the pericardium in 2 patients. There was strong presumptive evidence of pericardial involvement in case 10 reported in this paper. Involvement of the kidney has been suspected in the sarcoid process during life (Nordin,¹⁷ Schaumann,³ and Rotenberg and Guggenheim¹⁸), but it has been found infrequently at autopsy (Spencer and Warren¹⁹). Two instances of isolated sarcoidosis of the small intestine, simulating nonspecific ileojejunitis, have been reported with the findings at operation (Watson, Rigler, Wagensteen and McCarthy²⁰). One of Longcope's patients had sarcoid disease of the testicles and epididymis, with a eunuchoid state.

13. Roos, B.: Cerebral Manifestation of Lymphogranulomatosis Benigna (Schaumann) and Uveoparotid Fever (Heerfordt), *Acta med. Scandinav.* **54**:123-130, 1940.

14. Kraus, E. J.: Sarcoidosis (Boeck-Besnier-Schaumann Disease) as Cause of a Pituitary Syndrome, *J. Lab. & Clin. Med.* **28**:140-144, 1942.

15. Nickerson, D. A.: Boeck's Sarcoid: Report of Six Cases in Which Autopsies Were Made, *Arch. Path.* **24**:19-29 (July) 1937.

16. Longcope, W. T., and Fisher, A. M.: Involvement of the Heart in Sarcoid, *J. Mt. Sinai Hosp.* **8**:784-797, 1942.

17. Nordin, G.: Maladie de Schaumann (lymphogranulomatose benigne) avec plaques erythrodermiques et iridocyclite comme symptomes cliniques dominants, *Acta med. Scandinav.* **104**:131-136, 1940.

18. Rotenberg, L., and Guggenheim, A.: Boeck's Sarcoid: Report of Case with Renal Involvement, *Dis. of Chest* **8**:392-395, 1942.

19. Spencer, J., and Warren, S.: Boeck's Sarcoid, *Arch. Int. Med.* **62**:285-296 (Aug.) 1938.

20. Watson, C. J.; Rigler, L. G.; Wagensteen, O. H., and McCarthy, J. D.: Isolated Sarcoidosis of the Small Intestine Simulating Non-Specific Ileojejunitis, *Gastroenterology* **4**:30-50, 1945.

description of the characteristic bony changes on roentgen study and Heerfordt's⁵ description of uveoparotid fever are notable contributions.

PATHOLOGIC ANATOMY

Little is known of the pathogenesis of the disease. Schaumann³ in 1924 discussed the relationship to tuberculosis and the different states of immunity present in the two diseases as indicated by the sensitivity of the skin to tuberculin. In 1936 he raised the question of a pleomorphic variant of the tubercle bacillus as the cause of sarcoid. This work has not been substantiated by other investigators.

Tubercle bacilli have been found by several workers in sarcoid lesions; however, the question always remains as to whether or not the patient had the two diseases concomitantly. The presence of tubercle bacilli in lesions of sarcoid has been reported by Rubin and Pinner,⁶ Hollister and Harrell,⁷ Reisner⁸ and Dorgeloh and Tully.⁹ Goeckerman¹⁰ once thought that tubercle bacilli could be found only in the early lesions. In a number of cases which have been followed over a period of years, frank tuberculosis has been seen to develop in conditions clinically and histologically diagnosed as sarcoid. The development of tuberculosis is one of the frequent causes of death in sarcoid, and the relationship is thought to be more than coincidental by most writers (Pinner,¹¹ Rubin and Pinner⁶, Reisner,⁸ Schaumann³ and Harrell¹²). However, it must be admitted that definite proof of the tuberculous nature of sarcoid is still lacking.

In 1914 Schaumann³ described involvement of the tonsils in nearly all the patients examined by him. Enlargement of the tonsils was noted in only 2 of our patients. One of these had his tonsils removed elsewhere, while the other had them removed at our hospital and the lesions

5. Heerfordt, C. F.: Ueber eine "Febris uveo-parotidea subchronica" an der Glandula Parotis und der Uvea des Augus lokalisiert und häufig mit Paresen cerebrosponialer Nerven kompliziert, *Arch. f. ophth.* **70**:254-273, 1909.

6. Rubin, E. H., and Pinner, M.: Sarcoidosis: Case Report and Literature Review of Autopsied Cases, *Am. Rev. Tuberc.* **49**:146-169, 1944.

7. Hollister, W. F., and Harrell, G. T.: Generalized Sarcoidosis of Boeck Accompanied with Tuberculosis and Streptococcic Bacteremia, *Arch. Path.* **31**:178-181 (Feb.) 1941.

8. Reisner, D.: Boeck's Sarcoid and Systemic Sarcoidosis: A Study of Thirty-Five Cases, *Am. Rev. Tuberc.* **49**:289-307 and 437-461, 1944.

9. Dorgeloh, R., and Tully, P. W.: Relationship of Boeck's Sarcoid and Tuberculosis, *Arch. Path.* **40**:309-311 (Nov.-Dec.) 1945.

10. Goeckerman, W. H.: Sarcoid and Related Lesions, *Arch. Dermat. & Syph.* **18**:237-262 (Aug.) 1928.

11. Pinner, M.: Non-Caseating Tuberculosis, *Am. Rev. Tuberc.* **37**:690-720, 1938.

12. Harrell, G. T.: Generalized Sarcoidosis of Boeck, *Arch. Int. Med.* **65**:1003-1034 (May) 1940.

with only a few in the midzones of the lobules. In miliary tuberculosis the reverse is said to be true (Nickerson¹⁵). Endarteritis of the pulmonary vessels which resulted in failure of the right side of the heart was found in a patient at autopsy by Tice and Sweany.²⁶ In their patient the lesions of the pulmonary parenchyma were healed or healing when death occurred.

CLINICAL OBSERVATIONS

The manifestations of this disease are many and varied because of the number of organs and tissues which may be involved (Schaumann³ and Klemperer²⁷). In general, it may be said that about four clinical types are recognized as they present themselves to the physician. These are: (1) the sarcoids of the skin as described by Boeck and Besnier; (2) the uveoparotid fever of Heerfordt; (3) the type with lymphadenopathy of superficial or intrathoracic nodes simulating lymphoblastomas, and (4) a type in which there is primarily involvement of the pulmonary parenchyma on roentgen study and which, when there is also cough, loss of weight and slight fever, may closely resemble pulmonary tuberculosis.

The patients whose cases are presented here were admitted to an army general hospital between July 1, 1942 and April 1, 1946 (table 1). These patients were drawn primarily from young male military personnel. The hospital has functioned as a center for the treatment of tumors, and the majority of the patients sent there have symptoms simulating those of a malignant tumor. Indeed, all our patients had intrathoracic lymphadenopathy, and all except 2 had enlargement of the superficial lymph nodes. The result of this selection will immediately be seen when it is noted that 27 of the 28 patients were men, while the sex incidence in most of the previously reported series was about equal. Of the 35 cases reported by Reisner,⁸ only 7 patients were males and 24 were females. In Longcope's²⁸ 31 patients, the ratio of males to females was 18 to 13. In the present series the age incidence was undoubtedly influenced by the aforementioned factors. Twenty-two were in the third decade of life, 6 in the fourth, only 2 in the second and 1 in the sixth. Our youngest patient was a girl 13 years of age and our oldest a man of 58. Rubin and Pinner⁹ have reported an autopsy by Stein on a women of 68 years. This represents an extreme range. The majority of the patients have been in the young adult group. It is

26. Tice, F., and Sweany, M. C.: Fatal Case of Sarcoid with Autopsy Findings, *Ann. Int. Med.* **15**:597-609, 1941.

27. Klemperer, P., in *Proceedings of the Tumor Seminar of the American Society of Clinical Pathologists*, Philadelphia, June 7, 1942.

28. Longcope, W. T.: Sarcoidosis or Besnier-Boeck-Schaumann Disease, *J. A. M. A.* **117**:1321-1330 (Oct. 18) 1941.

In all the cases presented in this paper the diagnosis was made by histologic examination and confirmed by the Army Medical Museum. Since enlargement of the peripheral lymph nodes is common in this disease, an accessible lymph node can easily be removed. In our experience the cervical region has been the optimum site for removal of material for biopsy; however, the surgeon should not hesitate to remove small, innocent-appearing nodes, as these will frequently show the typical lesion. It is best to avoid the inguinal region in seeking material for biopsy, as the nodes in this region almost always show varying degrees of nonspecific inflammation and a definite diagnosis is difficult to establish. In addition to the peripheral lymph nodes, we have secured satisfactory material from the following structures: tonsils, parotid glands, lacrimal glands, skin and mediastinum. Aspiration of biopsy material from the liver was performed successfully in 11 of 14 cases by van Buchem.²¹ He recommended it when other sources were not available.

Microscopically there is proliferation of the epithelioid cells, with the formation of granulomas. Giant cells of the Langhans type are present. The rare occurrence of peculiar basophilic cytoplasmic inclusions in giant cells has been described (Moore²²). In the lymph nodes the granulomas are arranged in clusters which may fill the entire node, but they usually do not break through the capsule. Lesions have been found to undergo fibrosis and replacement with hyalinized connective tissue (Bruce and Wassen²³), and the presence of a large amount of collagen is taken to indicate a healing or healed process (Nicker-son¹⁵), although King²⁴ questioned the statement that the sarcoids are replaced by fibrous tissue. The center of these tubercles may show slight necrosis, but true caseation is rare.

In a study of the bone marrow of 3 patients, Lucia and Aggeler²⁵ found a picture simulating a chronic infectious process. There was no evidence of depression of hemopoiesis in the marrow. A normal marrow was found in the single case studied by us. In the liver it has been noted that the lesions of sarcoid are more numerous in the portal triads,

21. van Buchem, F. S. P.: On Morbid Conditions of the Liver and the Diagnosis of the Disease of Besnier-Boeck-Schaumann, *Acta med. Scandinav.* **123**:151-153, 1946.

22. Moore, R. A.: *A Textbook of Pathology*, Philadelphia, W. B. Saunders Company, 1944, pp. 544-545.

23. Bruce, T., and Wassen, E.: Clinical Observations on Course and Prognosis of Lymphogranulomatosis Benigna (Schaumann), Particularly in Regard to Pulmonary Lesions, *Acta med. Scandinav.* **104**:329-343, 1940.

24. King, D. S.: Sarcoid Disease as Revealed in the Chest Roentgenogram, *Am. J. Roentgenol.* **45**:505-512, 1941.

25. Lucia, S. P., and Aggeler, P. M.: Sarcoidosis (Boeck): Lymphogranulomatosis Benigna (Schaumann) Observations on the Bone Marrow Obtained by Sternal Puncture, *Acta med. Scandinav.* **104**:351-365, 1940.

TABLE 1.—*Clinical Observations—Continued*

Case	Age (Yr.), Sex, Race	Complaints	Superficial Nodes	Eyes	Comments
21	22 M N	Parotid swelling and fever	Femoral	Uveitis; lacrimitis
22	23 M W	None	Axillary	Negative	Gunshot wound in the thigh
23	29 M W	Dyspnea, cough and hemoptysis	Generalized	Negative	Endamoeba histolytica present
24	20 M N	Chronic cough and dyspnea	Generalized	Negative
25	38 M N	Loss of weight (50 pounds), pain in the chest and cough	Generalized	Negative
26	24 M N	None	Cervical and inguinal	Negative
27	24 M N	Dyspnea and fatigability	Generalized	Negative	Biopsy of material from the tonsil showed the presence of sarcoidosis; deviation of the right axis in the electrocardiogram
28	22 M N	Parotid swelling	Generalized	Uveitis	Tall P waves in the electrocardiogram; the parotid gland was shown to be infected on biopsy

significant, however, that 15 of our 28 patients were Negroes. This was much higher than the over-all ratio of Negro to white patients admitted to the hospital and is in accord with the experience of others (Longcope,²⁸ Harrell,¹² Thomas²⁹ and Pinner¹¹). In European countries the disease is said to be frequent among the Scandinavian people (Hannesson³⁰).

The symptoms which these patients present are variable in degree and tend to be mild. Nine of them complained of cough which was persistent and productive of only a small amount of sputum: Only 2 patients had slight hemoptysis. Eleven complained of dyspnea which was aggravated by exertion, particularly long marches or field exercises, while only 6 had mild pain in the chest. Six of them had lost a significant amount of weight, the greatest reported being 50 pounds (23 Kg.). Weakness, fever, anorexia, nausea and vomiting were occasional symptoms. Three patients had symptoms referable to the eyes only. It is noteworthy that 6 persons had no symptoms whatsoever, their disease having been discovered only by routine roentgenologic study of the chest. It was observed that cough and dyspnea were the most frequent presenting symptoms. This was probably due to the fact

29. Thomas, C. C.: Sarcoidosis, Arch. Dermat. & Syph. 47:58-73 (Jan.) 1943.

30. Hannesson, H.: Besnier-Boeck's Disease; Review, Brit. J. Tuberc. 35:88-113, 1941.

TABLE 1.—*Clinical Observations*

Case	Age (Yr.), Sex, Race	Complaints	Superficial Nodes	Eyes	Comments
1	26 M N	Dyspnea and cough	None	Normal	Electrocardiogram showed right axis deviation; cor pulmonale seen at autopsy
2	20 M W	Night sweats, loss of weight and cough	Axillary and inguinal	Lacrinitis	Biopsy showed normal bone marrow; biopsy of a lymph node suggests sarcoid
3	13 F W	Fever, loss of weight (25 pounds) and anemia	Generalized	Uveitis and keratitis	Enlarged spleen; parotitis; nephritis; necrosis with caseation on biopsy
4	22 M W	Pain in the eyes and blurred vision	Axillary and inguinal	Iridocyclitis	No response to roentgen therapy with 1,350 r.
5	31 M N	Cough and weakness	Axillary	Normal	Chronic tonsillitis
6	21 M N	Pain in the chest, cough and loss of weight (25 pounds)	Generalized	Normal	Normal electrocardiogram; bronchoscopy non-contributory
7	26 M N	Pain in the chest, fever, cough and dyspnea	Cervical (slight)	Iridocyclitis	Fever throughout course; nodules on the skin of legs and forearms
8	23 M N	Dyspnea and cough	Generalized	Normal	Normal electrocardiogram
9	21 M W	Chronic cough	Supraclavicular	Conjunctivitis	Amputee; tubercles with necrosis on biopsy
10	31 M W	Dyspnea, cough and pain in the chest	Generalized	Normal	No response to roentgen therapy with 1,300 r.; deviation of the right axis in the electrocardiogram; pericarditis, with effusion
11	21 M W	Pain in the chest, chest, cough and dyspnea	Generalized	Normal	Endamoeba histolytica present; deviation of the left axis in the electrocardiogram
12	18 M W	None	Cervical	Normal
13	21 M W	Loss of weight (50 pounds), nausea and vomiting	Generalized	Uveitis
14	25 M N	Loss of weight, headaches and edema	Generalized	Normal
15	25 M W	None	Supraclavicular	Normal Normal	Spleen palpable
16	27 M W	None	Epitrochlear	Normal
17	58 M W	Weakness, anemia and dyspnea	None	Negative	Splenectomy in 1945 for hemolytic anemia
18	25 M N	Dyspnea	Postauricular	Iridocyclitis; lacrinitis	Positive reaction to Kahn test for syphilis
19	19 M N	Dyspnea	Generalized	Lacrinitis; uveitis	Normal electrocardiogram
20	34 M N	None	Inguinal	Lacrinitis	Skin of the eyelids involved

TABLE 2.—Laboratory Observations

Case	Tuberculin Test, Reaction	Red Blood Cell Count*	Hemo- globin Content*	White Blood Cell Count*	Differential Count				
					Eosino- phils	Mono- cytes	Cal- cium, Mg.	Phos- pha- tase	Al- kaline Phos- phatase
1	Negative (0.1 mg.).....	3.8 5.2	70% 100%	4.6 13.6	0 ..	0 ..	10.5 11.5	2.8 3.0	1.4 5.6
2	Negative.....	4.3	82%	4.4	2	3
3	Negative (patch test).....	4.0 4.7	73% 85%	3.7 7.8	2 7	0 12	11	3.5 5.3	6.1 6.7
4	4.9 5.4	90% 110%	3.0 7.3	0 4	0 8
5	4.4
6	Positive (0.00002 mg.).....	4.3 5.1	84% 94%	5.6 9.1	1 13	0 10	10 11.5	3.3 3.6	5.4 7
7	Negative (patch test).....	3.7 5.0	80% 90%	3.0 9.5	0 4	0 3	11	4 ...	1.6 ...
8	Negative (patch test).....	4.4 5.3	100%	3.9 6.8	0 4	0 6	11	3.2 ...	5.0 ...
9	Negative.....	4.7 5.4	99% 112%	3.4 7.5	1 11	1 5
10	3.7	75%	11.0
11	Negative (0.00002 mg.).....	3.9 4.8	95% 96%	5.1 10.0	0 4	0 1	10.5	4.0 ...
12	Negative.....	5.2	5.4
13	Negative (patch test).....	3.7 4.5	71% 83%	7.6 15.3	1 8	0 7	9.5	3.0
14	Negative (patch test).....	4.0 4.5	81% 85%	4.7 6.6	0 8	0 2	10.5	3.6 ...	5.7 ...
15	Positive (weak).....	5.3	2	4
16	Negative.....	5.5 ...	110%	7.1 7.2	7 8	0 ..	8.5 11.5	5.4 8.9	1.4 3.1
17	Negative (patch test) and test with purified protein derivative.....	2.6 3.3	55% 73%	9.9 19.3	2 9	0 2	11.2	5.5
18	2+ positive (0.00002 mg.)....	4.9 ...	13 Gm. 14 Gm.	5.8 8.8	2 6	0 7	9.7	2.9 ...	8.0 ...
19	Negative (0.00002 mg.).....	4.2 4.6	11.5 Gm. 12 Gm.	8.5 10.9	0 6	0 6	8.5 9	3.8 ...	8.8 10.2
20	2+ positive (0.00002 mg.)...	4.9 ...	92% 95%	6.0 6.4	0 7	2 4	11.0	3.1 ...	9.2 ...
21	Negative (.000002 mg.).....	4.2 4.6	85% 96%	4.5 8.4	0 13	1 6	11.8	3.2 ...	6.8 ...
22	Negative (patch test) and test with purified protein derivative.....	4.0 5.1	13.6 Gm. 14.5 Gm.	6.2 11.3	0 5	0 5
23	Negative (patch test).....	5	..	10.5	5	6
24	Negative (patch test).....	4.7	100%	8.4	12	3
25	Negative (patch test) and test with purified protein derivative.....	5.0 ...	98% 105%	5.0 6.0	1 4	0 0
26	Negative (patch test).....	4	4.4
27	Negative (0.00002 mg.).....	4.0 5.9	85% 102%	5.2 9.6	0 12	0 7	10.6	3.4
28	Negative (patch test) and test with purified protein derivative.....	4.4 5.5	87% 105%	4.6 9.0	3 5	3 7

* When several determinations were made the high and low values are given.

that all patients had intrathoracic disease. The peripheral lymph nodes were found to be enlarged in 26 of the 28 patients. The palpable nodes were small and discrete and did not tend to be confluent; in fact, the involvement of the lymph nodes was so slight in some patients as to seem clinically insignificant, so that the surgeon was often reluctant to perform a biopsy until urged to do so by the medical service. Not infrequently one of these "insignificant nodes" showed the characteristics of the disease. Reisner⁸ has reported superficial lymphadenopathy in nearly 100 per cent of his series. This was also a constant finding in the series reported by Longcope²⁸ in 1941.

Involvement of the eye was observed in 11 of our patients. The lesion was most often a uveitis or iridocyclitis, but any or all of the structures of the eye may be involved (Levitt³¹). The ocular manifestations were as follows: uveitis in 7 cases, lacrimitis in 3, keratitis in 1 and conjunctivitis in 1. Only 3 patients had the characteristic combination of ocular disease and swelling of the parotid gland as described by Heerfordt⁵ in the so-called uveoparotid fever. Moderate enlargement of the spleen occurred only three times. Reisner⁸ expressed the belief that the enlargement of the spleen occurs early in the disease and then tends to undergo regression. In only 2 instances were we able to find a cutaneous lesion. In 1 of these (case 8) there was a small nodule on the forehead, which the patient stated had been present for ten years; when removed, this showed definite changes typical of sarcoid. The other patient had enlarged mediastinal lymph nodes and fever. No definite diagnosis could be made because there were no palpable lymph nodes or any obvious source for pathologic study. Repeated careful palpation of the cutaneous surface finally revealed nodules on the legs and forearms, two of which were removed and showed the characteristic structure of the disease (case 7). This low incidence of cutaneous lesions is undoubtedly due to the factors operating in the selection of these patients as described previously. A significant degree of fever, not accounted for by intercurrent infections or other disease, was present in 8 instances. The fever was usually of low grade and continued over a period of several days or weeks. Only 1 patient had hyperpyrexia over a period of three months (case 7).

LABORATORY OBSERVATIONS

Perhaps the most consistent of all the laboratory observations in this disease is the reaction to the tuberculin skin test, which in a great majority of instances is negative. This test was done in 25 of our cases, and the reaction was negative in 21, doubtful in 2 and weakly positive (2 plus) in another 2 (table 2). This anergy to tuberculin has been

31. Levitt, J. M.: Boeck's Sarcoid with Ocular Localization, *Arch. Ophth.* 26:358-389 (Sept.) 1941.

liferation of the reticuloendothelial system. This is notably true in lymphogranuloma venereum, multiple myeloma and kala-azar. The Frei test gave a negative reaction in the 4 instances in which it was done.

An elevation of the blood calcium and alkaline phosphatase levels in sarcoidosis was described by Harrell and Fisher.³³ The calcium content was determined by the Clark-Collip modification of the Kramer-Tisdall method in 16 patients, and it was above 10.5 mg. in 10 (table 2). It should be noted that 8 of these also had hyperproteinemia. This eleva-

Laboratory Observations Continued—Table 2-B

Case	Albumin	Globulin	Miscellaneous Laboratory Tests
15	4.3	2.4	Agglutination test for brucellosis gave a negative reaction
	4.5	2.7	
16	4.1	2.2	Sedimentation rate normal; coccidioidin test gave a negative reaction
	5.4	3.4	
17	3.3	5.2	Reaction to the cephalin flocculation test was positive (3+)
	4.0	3.3	
18	3.4	3.4	Sedimentation rate normal; test for heterophile antibodies and agglutination test for brucellosis gave negative reactions
	4.4	2.4	
	3.9	3.0	
19	3.6	4.3	Reactions to the test for heterophile antibodies and to the coccidioidin and Frei tests were negative
	3.5	2.4	
	4.7	3.1	
	3.5	4.3	
20	5.2	3.2	Sedimentation rate normal; Frei test, test for heterophile antibodies and coccidioidin test gave negative reactions
	4.0	2.2	
21	3.0	3.7	Sedimentation rate normal
	3.4	3.5	
22	5.0	2.5	Agglutination test for brucellosis, test for heterophile antibodies and coccidioidin test gave negative reactions
23	4.4	3.6	Reactions to test for heterophile antibodies and to the Frei test were negative
24	3.7	2.5	Test for heterophile antibodies gave a negative reaction
25	2.8	3.7	Cholesterol content 264 mg., esters 73.9%; reaction to the test for heterophile antibodies negative; sedimentation rate normal
	3.9	2.8	
26	4.1	2.1	Test for heterophile antibodies gave a negative reaction; cholesterol content 240 mg.
27	4.3	2.7	Reaction to the Frei test was negative
28	4.4	2.4	Sedimentation rate elevated; agglutination test for brucellosis gave a negative reaction
	4.4	2.8	
	3.5	3.3	

tion may be due to the calcium-binding power of the blood proteins, as discussed by Jaffe and Bodansky.³⁴ Fourteen determinations of the alkaline phosphatase of the blood were made by the modified King-Armstrong method. In only 5 instances were the readings higher than 6 Bodansky units, the highest single figure being 10.2 Bodansky units.

33. Harrell, G. T., and Fisher, S.: Blood Chemical Changes in Boeck's Sarcoid with Particular Reference to Protein, Calcium and Phosphatase Values, *J. Clin. Investigation* **17**:687-691, 1939. Harrell, G. T.: Generalized Sarcoidosis, *J. Bowman-Gray School Med.* **1**:1-4, 1943.

34. Jaffe, H. L., and Bodansky, A.: Serum Calcium; Clinical and Biochemical Considerations, *J. Mt. Sinai Hosp.* **9**:901-920, 1943.

noted by many writers. It has led to the theory that sarcoidosis is an atypical response of the reticuloendothelial system to the tubercle bacillus. In Reisner's⁸ series the incidence of positive reactions was 40 per cent; however, when a positive reaction does occur it is usually weak and occurs only with the higher concentrations of tuberculin. Reisner tested 10 patients with 10 mg. of old tuberculin and obtained negative reactions in all. The tuberculin test should always be done and is of some value in the differential diagnosis. Another interesting and significant symp-

Laboratory Observations Continued—Table 2-A

Case	Albumin, Gm.	Globulin, Gm.	Miscellaneous Laboratory Tests
1	3.8 5.0	2.9 3.0	Sedimentation rate elevated
2	3.5	5.2	Agglutination test for brucellosis gave a negative reaction
3	4.0 3.1	3.9 2.9	Sedimentation rate elevated
4	4.7	3.3	Spinal fluid sterile
5	3.6 4.5	3.0 1.5
6	5.5 4.1 4.1	3.4 5.1 2.1	Cholesterol content 184 mg.
7	4.0 4.4 5.5 4.7	2.9 3.6 2.5 2.0	Reaction to test for heterophile antibodies negative
8	4.6 4.3	3.4 3.7	Cholesterol content 194 mg.
9	4.3 4.5 5.5	1.4 2.3 1.4	Reaction to test for heterophile antibodies negative; agglutination test for brucellosis gave a negative reaction
10
11	5.2 4.6	2.1 2.7	Agglutination test for brucellosis gave a negative reaction; sedimentation rate elevated
12	4.7	3.9	Sedimentation rate elevated
13	4.4 4.3	3.3 4.0	Sedimentation rate elevated; reaction to test for heterophile antibodies positive (3+ [1:112], 1+ [1:224])
14	4.4	3.6	Agglutination test for brucellosis gave a negative reaction, as did the test for heterophile antibodies; sedimentation rate elevated

tom, when present, is the elevation of the globulin fraction of the blood protein (table 2). A study of the blood protein was carried out in 27 of the 28 cases by the standard method of digestion and nesslerization. If the figures given for average normal by Peters and Van Slyke are followed³² (total protein 7 Gm. per hundred cubic centimeters, with albumin 4.44 Gm. and globulin 2.58 Gm.), the total protein was above this figure in 19 and the globulin level elevated in 23 patients. It is interesting in this connection that elevation of the globulin fraction of the blood protein has been described in diseases associated with pro-

32. Peters, J. P., and Van Slyke, D. D.: Quantitative Clinical Chemistry, Baltimore, Williams & Wilkins Company, 1931, vol. I.

ROENTGENOLOGIC STUDY

In all 28 patients there was evidence of intrathoracic lymphadenopathy (table 3). Its presence is not always easily detectable. Examination should include careful roentgenoscopy, with a swallow of barium given to the patient during the course of the study. A posteroanterior

TABLE 3.—Roentgenologic Observations

Case	Intrathoracic Lymph Nodes*				Types of Pulmonary Infiltration*	Involvement of Hands*	
	Paratracheal		Peribronchial				
	Right Side	Left Side	Right Side	Left Side			
1	+	+	+	+	++ Reticular and nodular	++	
2	+	0	++	++	0	0	
3	++ -)0	+ -)0	++ -)0	++ -)0	+ Reticular	++	
4	++	++	++	++	+ Reticular and nodular	0	
5	+	+	+	+	+ Nodular	++	
6	++	+	+	+	0 Pleural, with inter- lobar effusion	0	
7	++	++	++	++	0	0	
8	++	+	++	++	+ Ret:cular	0	
9	++ -)+	++ -)+	++ -)+	++ -)+	0	0	
10	+	+	+	+	0 Pericarditis and pleural effusion	0	
11	++	+	+	+	0	0	
12	+	+	+	+	0	Not examined	
13	++	+	++	++	+ Nodular and reticular		
14	++	+	0	0	0	0	
15	++	+	+	+	+ Reticular	0	
16	+	0	0	0	++ Reticular and nodular	0	
17	++ -)+ ++	++ -)+ ++	+	+	+ Reticular	+	
18	+	0	++	++	0	0	
19	+	+	++	++	++ Reticular and nodular	0	
20	+	+	++	++	0	0	
21	+	0	++	++	0	+	
22	++	0	++	++	+ Reticular	0	
23	++	++	++	++	+	Reticular	0
24	+	+	+	+	+	Reticular and nodular	0
25	++	++	++	++	0	0	
26	++	+	++	++	0	0	
27	+	0	0	0	+	Reticular and nodular	0
28	++	+	+	+	+	Reticular and nodular	+

* 0 indicates absent, + slight to moderate, ++ pronounced and — change while under observation.

and lateral examination should be made, together with such oblique views as are deemed necessary. A Bucky-Potter diaphragm will aid in the delineation of the trachea and the major bronchi, and a laminagram may be of value in selected cases. With this careful technic, nodes of 2 cm. in diameter or greater will be detected. Nodes smaller than this will most likely not be seen even with the best technic available at the present time because of the density of the overlying structures. In our

Total and differential white blood cell counts were recorded one hundred and eight times in the 28 cases (table 2). Of these counts, only ten were below 4,500 cells. Only 7 patients had any single count below this figure, and in them it was not consistently low. Thus 21 patients showed no leukopenia. The great majority of the blood counts were normal, with elevations from time to time during the course of the disease, usually with some intercurrent infection. This finding differs somewhat from that of Reisner,⁸ who found leukopenia in one third of his cases; 16 of Longcope's²⁸ 28 patients had counts between 3,000 and 6,000. Longcope and Pierson³⁵ have described eosinophilia. In our series 7 patients had an eosinophil count of 5 per cent or more, while in 5 instances single counts of 10 per cent or above were recorded. The monocytes were not consistently increased as has been reported by Harrell,¹² although occasionally single counts as high as 9 to 12 per cent were seen. One patient (case no. 1) who died and on whom necropsy was performed was followed over a period of one year. He showed in a total of twelve white blood cell counts no significant deviation from normal in any value except for one total leukocyte count of 13,000, which occurred during a febrile period associated with hemoptysis. A total of eighty-two determinations of the red blood cell count and the hemoglobin content were made in the 28 cases. In only 2 was the erythrocyte count below 4,000,000 (cases 3 and 17). In 1 of these (case 17), the patient, a man 58 years of age, had previously undergone splenectomy for acquired hemolytic jaundice.

A few other laboratory observations showed no significant changes. The agglutination test for brucellosis elicited a negative reaction in 8 patients, and the reaction to the coccidioidin skin test was negative in 5. The agglutination test for heterophile antibodies was done in 12 patients, and the reaction was negative in 11; 1 patient had a slightly positive reaction. In the majority of the patients studies of sputum and gastric washings for tuberculosis and fungi were made, and in all instances the results were negative. Inoculation of animals for tuberculosis was not done. There was no instance of an increase in the nonprotein nitrogen or blood cholesterol. No Bence Jones protein was found in the urine. The Kahn test was performed on all patients in this series and elicited a negative reaction in all except 1, who presented clinical evidence of syphilis. This is in contrast to Reisner's⁸ series, in which the reaction to the Wassermann test was positive ten times and doubtful twice in 35 patients. This led him to believe that the disease might account for a false positive reaction, which conclusion we were unable to confirm. The sedimentation rate was determined in 12 patients and found to be increased in 8.

35. Longcope, W. T., and Pierson, J. W.: Boeck's Sarcoid (Sarcoidosis), *Bull. Johns Hopkins Hosp.* 60:223-295, 1937.

bronchi (fig. 8), but in no instance was there evidence of lobar collapse. Although the esophagus may be compressed or displaced by the mediastinal mass, there was no involvement of the esophageal wall in our series. In no case was there evidence of involvement of the phrenic nerves. Diaphragmatic paralysis is not an unusual occurrence in carcinoma of the lung, with spread to the peribronchial lymph nodes, and its absence helps to exclude bronchiogenic carcinoma.

With involvement of the intrathoracic lymph nodes, the differentiation of the relatively benign disease of sarcoid from the malignant forms of lymphogranuloma must be made. It should be clearly noted that enlargement of the right paratracheal nodes or group of nodes is of no value in making the differential diagnosis, as was once proposed (Kirklin and Hefke,³⁶ Wessler and Greene³⁷ and Williams³⁸). It will be seen with equal frequency in both types of lesion (fig. 9). Our experience has been confirmed by others (Wolpau, Higley and Hauser³⁹). However, in 11 of our cases the lymph nodes on the right

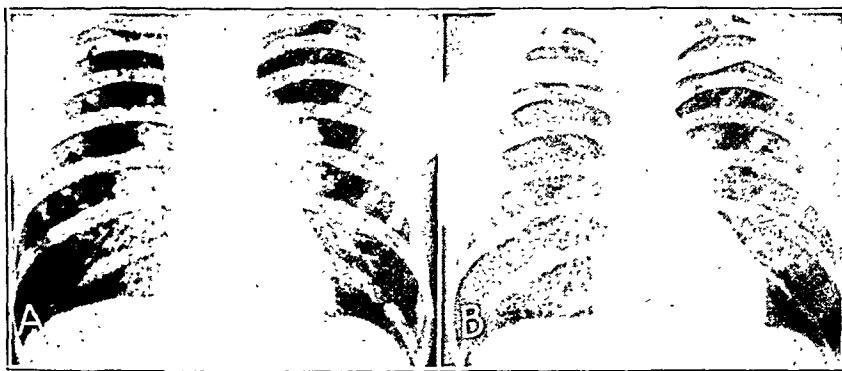


Fig. 2 (case 3).—*A*, roentgenogram taken on April 14, 1945, when the patient first appeared in the hospital. There is decided enlargement of the peribronchial and paratracheal lymph nodes. A fine reticular infiltration is present throughout both pulmonary fields. The unusual finding of calcification within the lymph nodes is present. *B*, eleven months later there has been a considerable regression of the peribronchial lymph nodes, suggesting a fibrous tissue replacement. The reticular pattern in both fields has been replaced by a gross nodularity.

side of the chest were larger and more numerous than those on the left. The reason for this is not apparent. It may be explained on the basis of the anatomic finding of Sukiennikow⁴⁰ that the nodes on the

36. Kirklin, B. R., and Hefke, H. W.: Roentgenologic Study of Intrathoracic Lymphoblastoma, *Am. J. Roentgenol.* **26**:681-690, 1931.

37. Wessler, H., and Greene, C. M.: Intrathoracic Hodgkin's Disease: Its Roentgen Diagnosis, *J. A. M. A.* **74**:445-448 (Feb. 14) 1920.

38. Williams, E. R.: Radiological Study of Intrathoracic Lymphogranuloma and Lymphosarcoma, *Brit. J. Radiol.* **8**:265-279, 1935.

39. Wolpau, S. E.; Higley, C. S., and Hauser, H.: Intrathoracic Hodgkin's Disease, *Am. J. Roentgenol.* **52**:374-388, 1944.

40. Sukiennikow, W.: *Topographische Anatomie der bronchialen und trachealen Lymphdrüsen*, Berlin 1903; cited by Miller.⁴¹

series the individual nodes varied in size from 2 to 5 cm. in diameter. Only occasionally were they larger than this. The increase in size of the paratracheal group parallels that of the peribronchial group. The bifurcation group of glands is probably similarly enlarged, but this is difficult to demonstrate. Bilateral involvement is the rule. Like the peripheral nodes, the intrathoracic nodes tend to remain discrete and do not have a tendency to coalesce. Pathologically, too, it has been noted that the sarcoid process has little tendency to break through the capsule. Consequently, in the roentgenogram the tumor will show a lobulated border because of the overlap of the adjacent nodes, giving strong evidence that it consists of a group of enlarged lymph nodes (fig. 4).

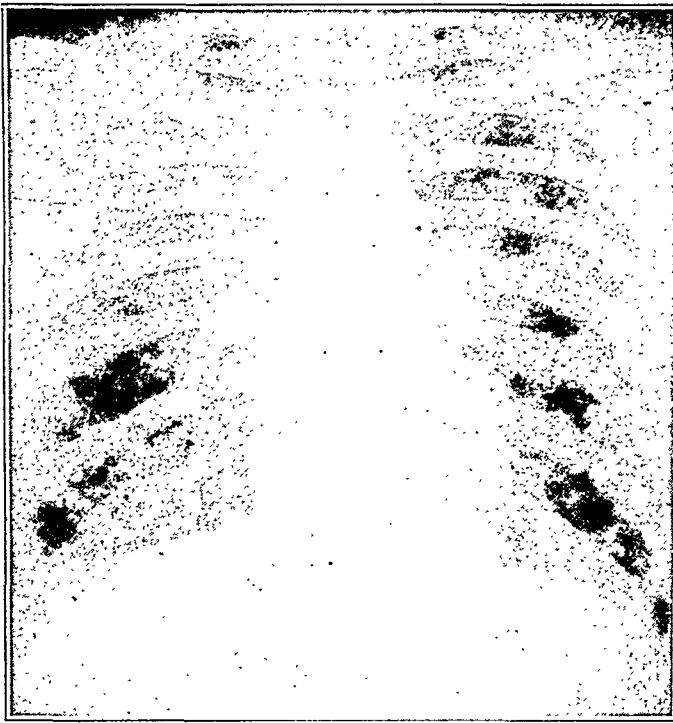


Fig. 1 (case 1).—Extensive nodular and reticular changes are seen throughout both pulmonary fields, and there is a slight enlargement of both the peribronchial and the paratracheal lymph nodes. The pulmonary parenchymal involvement became progressively more extensive and resulted in the development of failure of the right side of the heart, with death of the patient.

There was only 1 exception to this rule in our series, and as a result we were led to believe that it was a malignant process (fig. 5). Calcification in or about the nodes was also noted only once (fig. 2). This is interesting in view of the fact that Schaumann³ expressed the opinion that its presence indicates tuberculosis rather than sarcoid. The absence of calcification is of value in ruling out a multilocular dermoid cyst of the anterior mediastinum. In several patients we have been able to demonstrate a slight narrowing of the trachea or of one of the major

right side are greater in number than those on the left in the normal subject. This observation was confirmed by Miller,⁴¹ who also noted that there were a greater number of lymph nodes about the epiarterial bronchus than about the bronchi supplying the middle and lower lobes of the right lung.

Enlargement of the intrathoracic lymph nodes is found in the vast majority of cases of sarcoidosis. It was present in all our 28 cases, in 30 of 35 cases reported by Reisner⁸ and in 30 of 31 cases reported by Longcope.²⁸ In contradistinction, intrathoracic lymphadenopathy is a less frequent finding in malignant lymphoma, the incidence varying from 23 per cent (clasmatocytic type) to 61 per cent (Hodgkin's type) in a series of 618 cases studied by Gall and Mallory.⁴² Thus in a patient with enlargement of the peripheral lymph nodes the absence of involvement of intrathoracic lymph nodes on roentgen study favors a diagnosis of malignant lymphoma rather than of sarcoid.



Fig. 5 (case 6).—Posteroanterior and lateral views show a soft tissue tumor in the anterior-superior mediastinum. This is more prominent on the right side. The margins are straight, and the serrated border indicating a cluster of lymph nodes, usually seen in sarcoid, is missing. Also, there is evidence of fluid in the base of the right lung, with some fluid in the interlobular fissure and a slight degree of compression atelectasis of the lower lobe. The coalescence of the lymph nodes seen only in this patient led us to the erroneous conclusion that this was a malignant lymphoma.

In our experience the lymph nodes tend to remain discrete, presenting a well defined border. Later in the course of the disease the nodes regress slowly and spontaneously, to be replaced by fibrous tissue (figs. 2, 6 and 8). This impression of fibrous tissue replacement has been confirmed in cases coming to necropsy (Rubin and Pinner,⁶ Schu-

41. Miller, W. S.: *The Lung*, Springfield, Ill., Charles C Thomas, Publisher, 1937, chap. 8.

42. Gall, E. A., and Mallory, T. B.: *Malignant Lymphoma*, *Am. J. Path.* 18:381-429, 1942.

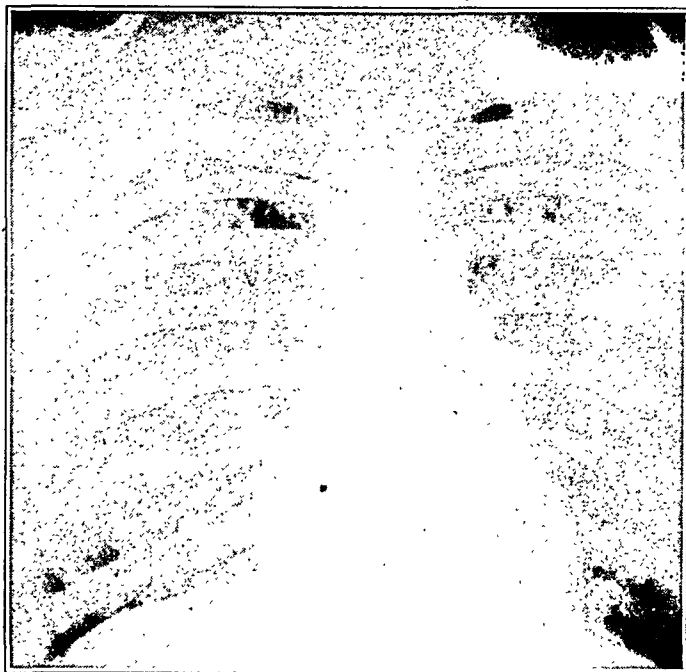


Fig. 3 (case 5).—Bilateral enlargement of the paratracheal and peribronchial lymph nodes is present, with a heavy, coarse, irregular infiltration scattered throughout both pulmonary fields.

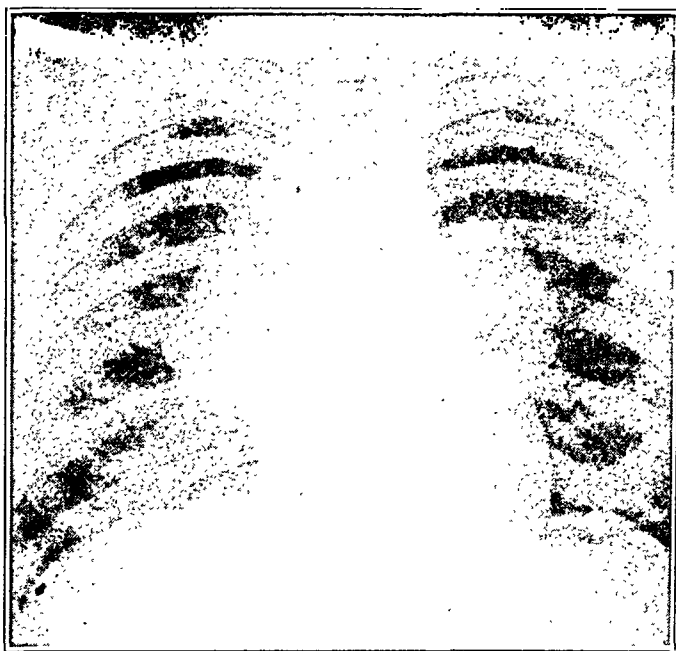


Fig. 4 (case 8).—Pronounced enlargement of the paratracheal and peribronchial lymph nodes is noted. There is a fine reticular infiltration throughout both pulmonary fields.

domycosis in the hospital in which this study was made, there are several reports in the literature which indicate that these two diseases may be confused (Kerley⁴⁷). Mediastinal lymphadenopathy will occur in coccidioidomycosis, being present in one sixth of all cases in which the disease is in the primary stage and in two thirds of those in which it is in the progressive stage (Lee, Nixon and Jamison⁴⁹). However, the thin-walled cavities in the lung described in coccidioidomycosis⁴⁹



Fig. 7 (case 10).—*A*, on April 23, 1943, there was bilateral enlargement of the paratracheal and peribronchial lymph nodes, with slight enlargement of the heart. *B*, on April 30 there has been a further increase in the size of the heart. It is globular in shape, and a zone of semitranslucency is seen about it. This is more marked about the left border. It was interpreted as pericardial fluid. *C*, on September 10 a pericardial aspiration was performed and air injected into the pericardium. Fluid levels are noted on both sides of the heart, with considerable thickening of the pericardium.

have not been seen in these cases of sarcoid. A history of residence in an area in which the disease is endemic, a positive reaction to the skin

49. Lee, R. V.; Nixon, N., and Jamison, H. W.: Syllabus on Coccidioidomycosis, Coccidioidomycosis Control Program for the Army Air Force Western Training Command, Headquarters Army Air Forces Western Flying Training Command, March 15, 1944.

mann³ and Cotter⁴³). In malignant lymphoma, however, the malignant process will tend to break through the capsule and invade the surrounding structures (Jackson and Parker⁴⁴), and hence the clearcut outline of the enlarged nodes is soon lost. Spontaneous regression of malignant lymphoma untreated by radiation can occur, but it is rare. Cavitation of the lung and the formation of bronchoesophageal fistula will occur in advancing Hodgkin's disease (Vieta and Craver⁴⁵), but these have not been found in uncomplicated sarcoidosis.

The roentgenographic appearance of the chest in erythema nodosum and sarcoidosis is similar. When intrathoracic lymphadenopathy is the only manifestation, it is impossible to distinguish between them by roentgen study alone (Paul and Pohle⁴⁶ and King²⁴), and a possible common etiologic relationship has been suggested by Kerley⁴⁷ and Vogt.⁴⁸ Although we have had no experience with pulmonary coccidioi-

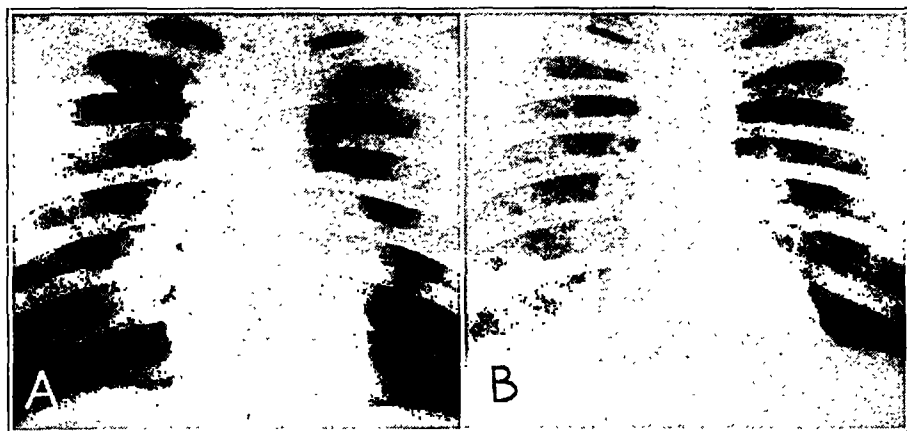


Fig. 6 (case 9).—*A*, on April 21, 1945 decided enlargement of the paratracheal and peribronchial lymph nodes was noted when the patient complained of a slight cough. He had been admitted to the hospital for a battle wound. These lymph nodes remained discrete, with well defined borders. This appearance is strongly suggestive of sarcoidosis. *B*, on Feb. 18, 1946, ten months later, the enlarged lymph nodes have undergone almost complete spontaneous regression, with fibrous tissue replacement. A faint, strandlike infiltration is now noted throughout both pulmonary fields.

43. Cotter E. F.: Boeck's Sarcoid: Autopsy in Case with Visceral Lesions, *Arch. Int. Med.* **64**:286-295 (Aug.) 1939.

44. Jackson, H., and Parker, F.: Hodgkin's Disease: II. Pathology, *New England J. Med.* **231**:35-43, 1944.

45. Vieta, J. O., and Craver, L. F.: Intrathoracic Manifestations of Lymphomatoid Diseases, *Radiology* **37**:138-158, 1941.

46. Paul, L. W., and Pohle, E. A.: Mediastinal and Pulmonary Changes in Erythema Nodosum, *Radiology* **37**:131-137, 1941.

47. Kerley, P.: Significance of Radiologic Manifestations (in Chest) of Erythema Nodosum (Relation to Sarcoidosis), *Brit. J. Radiol.* **15**:155-165, 1942.

48. Vogt, J. H.: Tuberculin Negative Erythema Nodosum, *Acta med. Scandinav.* **123**:151-153, 1946.

vessels which point toward the hilus. Pulmonary changes in sarcoid frequently pose a difficult problem in diagnosis. About equal involvement of both lungs is the rule. As was first shown by Schaumann,³ the changes are limited to the lymphatic vessels and lymphoid tissues of the reticuloendothelial system. The lungs are abundantly supplied with lymphoid tissue.⁴¹ This lymphoid tissue is in close association with the bronchi, blood vessels and pleura; consequently, no definite pattern of the changes in sarcoidosis can be predicted. Furthermore, the appearance of the chest at any one time will depend on the stage of the disease. The statement of Kirklin and Morton⁵¹ that the middle and lower thirds of the pulmonary fields are usually infiltrated has not been borne out in our series in which changes in the upper third of the lungs were noted with equal frequency.

Pulmonary parenchymal involvement was seen in 15 of the 28 cases (table 3). This is not a reliable index of the incidence of parenchymal involvement in sarcoidosis, as the period of observation in some of our patients was limited to a few months. The true incidence may be much higher than this, parenchymal involvement being seen in 33 of 35 cases reported by Reisner.⁸ The involvement is of two main types, which are frequently coexistent. The first and commonest is a reticular type, with thin strandlike areas of increased density extending out from the hilus (figs. 2 A, 4 and 6 B). This type was seen in all but 1 of the cases with parenchymal involvement recognizable roentgenographically. It probably represents involvement of the interlobular lymphatic vessels, as in the patient on whom autopsy was performed by Schaumann.³ It must be differentiated from a lymphatic spread of pulmonary metastases, pulmonary congestion secondary to cardiac failure and silicosis. Mueller and Sniffen⁵² showed that lymphangitic carcinomatosis is usually characterized by an irregular network of increased density in which are interspersed numerous small nodules. In congestive heart failure the basal portion of the lung is most heavily involved. Enlargement of the paratracheal lymph nodes is rare in silicosis, and an occupational history would aid in ruling out this disease. Less frequently a nodular increase in density throughout both pulmonary fields is observed; it was noted in 9 of 15 cases (figs. 1, 3 and 9 B). These nodules are of variable size and slightly irregular in outline. The slight irregularity of the nodules is not due to an inflammatory reaction, which is generally absent, as shown by the postmortem studies of Rubin and Pinner.⁶ At this stage the disease may be confused with miliary tuberculosis. In the

51. Kirklin, B. R., and Morton, S. A.: Roentgenological Changes in Sarcoid and Related Lesions, *Radiology* **16**:328-331, 1931.

52. Mueller, H. P., and Sniffen, R. C.: Roentgenologic Appearance and Pathology of Intrapulmonary Lymphatic Spread of Metastatic Cancer, *Am. J. Roentgenol.* **53**:109-123, 1945.

test for coccidioides infection or the culture of the fungus from the sputum would aid in making the differential diagnosis

In this study the earliest manifestation of the disease seemed to be enlargement of the intrathoracic lymph nodes. After a variable length of time, these tend to regress spontaneously, while parenchymal involvement apparently increases (figs. 2, 6 and 8). For this reason some authors have postulated a retrograde lymphatic spread (Bruce and Wassen²³ and Castleman⁵⁰), although Miller⁴¹ in his excellent study

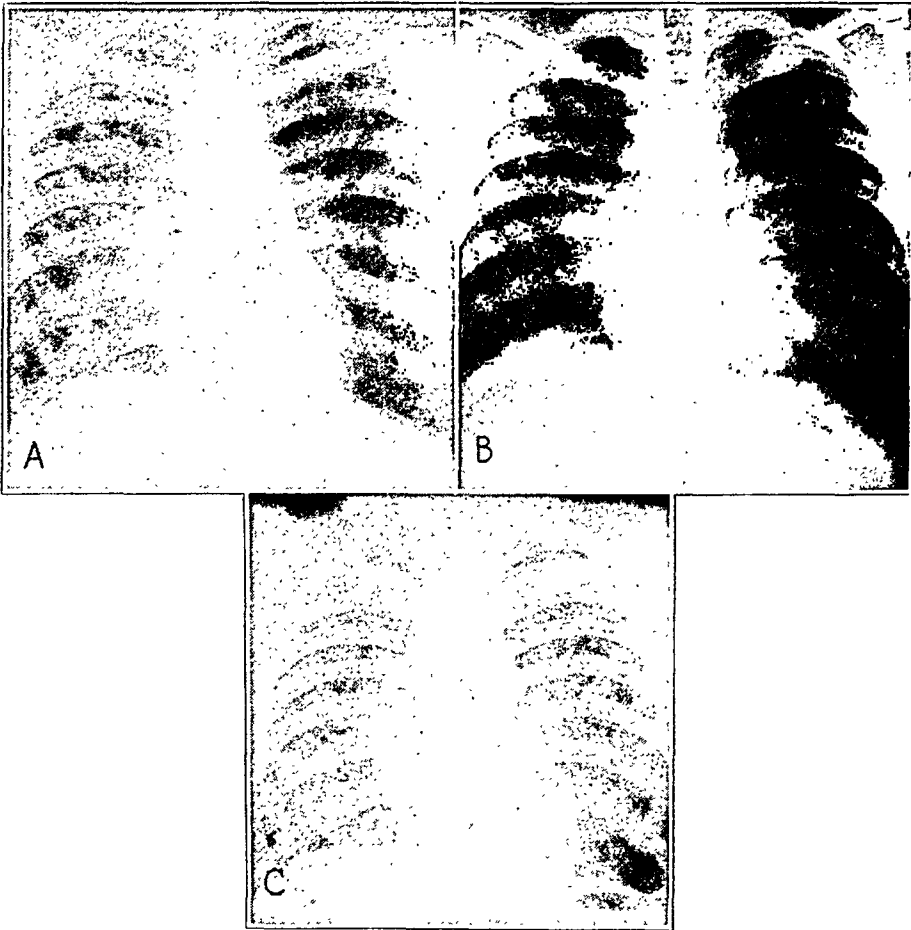


Fig. 8 (case 13).—*A*, on the first examination, on July 16, 1945, enlargement of the paratracheal and peribronchial lymph nodes is noted. *B*, an overexposed film made with a Bucky-Potter diaphragm shows narrowing of the lower lobe of the right lung, probably due to compression of the enlarged lymph nodes. However, atelectasis as a result of bronchial compression was not found in this series. *C*, on September 7 the enlarged lymph nodes showed beginning fibrosis, and a reticular and nodular infiltration was then noted in both pulmonary fields.

makes the unequivocal statement that an ebb and flow of the lymph does not occur, this being effectively prevented by the valves of the lymphatic

50. Sarcoid of Mediastinal Lymph Nodes, Cabot Case 30331, New England J. Med. **231**:268-269, 1944.

be justified because of its diagnostic value. None of the 6 patients had any symptoms referable to the bony changes, which were picked up on routine examination. The osseous involvement appears to be of two types, which, however, may be coexistent. The first is a diffuse rarefaction, with a reduction in the number of the bony trabeculae in the medullary portion of the bone and a slight thinning of the cortex (fig. 11 *B* and *C*). The other type consists of small oval defects, usually found at the heads or bases of the middle and proximal phalanges (fig. 11 *A*). Jüngling⁵⁵ called these oval cystoides or cystlike. They are not true cysts but replacements of bone by small granulomas (Ellis⁵⁶). In the hands, sarcoid must be differentiated from tuberculous dactylitis, gout and leprosy. In tuberculous dactylitis there is a notable swelling of the soft tissue, destruction of bone and sinus formation, and occasionally the joint is involved. We have not seen this type of a reaction, but if sarcoid should prove to be an atypical type of tuberculosis this differential would be pointless. The foci of bone destruction in gout are

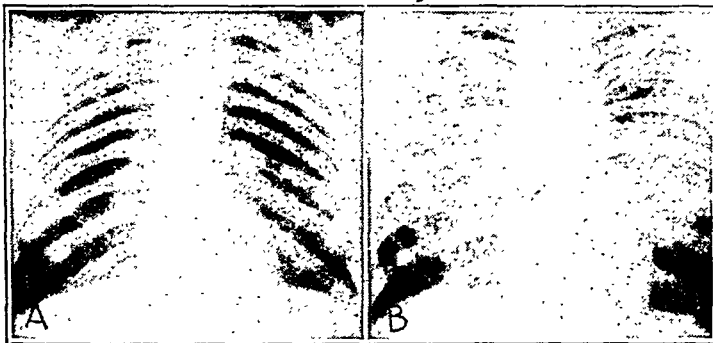


Fig. 9.—*A* (case 14), in this patient the discoverable enlargement of lymph nodes is limited to the paratracheal group, and this is more marked on the right side. Previous writers have considered this to be pathognomonic of Hodgkin's disease, but it appears that this was not so in our series. *B* (case 16), there is pronounced nodular and reticular infiltration throughout both pulmonary fields; yet this patient was asymptomatic, and the disease was discovered on routine examination of the chest. It illustrates the frequently made observation that in sarcoid the severity of the pulmonary symptoms is not related to the extent of pulmonary involvement.

more likely to be clearcut, punched-out areas usually in the metatarsals and phalanges, and a diffuse rarefaction of the bone as seen in sarcoid is not usual. Leprosy is usually accompanied by changes which are due to vascular insufficiency, as indicated by a progressive loss of bone substance beginning in the distal phalanges and progressing proximally. Since the bone marrow comprises a considerable portion of the reticulo-endothelial system, it is surprising that osseous lesions do not occur

55. Jüngling, O.: Ostitis tuberculosa multiplex cystica, *Fortschr. a. d. Geb. d. Röntgenstrahlen* **27**:375, 1920. Footnote 4.

56. Ellis, F. A.: Jüngling's "Ostitis Tuberculosa Multiplex Cystoides" Is Not Cystic Tuberculous Osteitis, *Acta med. Scandinav.* **104**:221-223, 1940.

latter the densities tend to be more discrete and more uniform in size, since they are the result of a shower of infected emboli. In sarcoid the lesions are less numerous and more widely spaced.

Owing to the predilection of the disease for the reticuloendothelial system, there must result considerable obstruction to the normal lymph flow in the lungs, with a corresponding disturbance of pulmonary physiology. Bruce and Wassen²³ found a uniform reduction in the vital capacity in their 6 cases, but they felt that this reduction was too small to explain the dyspnea from which their patients suffered. They believed that a thickening and narrowing of the walls of the blood vessels, as described by Schaumann³ and by Tice and Sweany,²⁶ is the more important factor. One death occurred in this series (case 1), and it was attributed to respiratory embarrassment, with resultant failure of the right side of the heart (fig. 1). Endarteritis of the pulmonary vessels, however, was not found in this patient. Although the mortality rate among patients with sarcoid is low, this has not been an uncommon sequence of events in the cases studied pathologically to date (Rubin and Pinner,⁶ Bernstein and Oppenheimer⁵³ and Longcope and Fisher.¹⁶ However, it should be reiterated that we were unable to correlate the degree of pulmonary involvement with the severity of symptoms in our series (fig. 9B).

Involvement of the heart and its covering is not unknown (Longcope and Fisher,¹⁶ Salvesen,⁵⁴ Cotter⁴³ and Schaumann³). In 1 of our patients (case 10) a pericardial effusion developed, and it was necessary to aspirate the pericardial sac on four occasions (fig. 7). In only 2 of our patients did a pleural effusion develop, and in neither was it extensive (figs. 5 and 7). With the known involvement and subsequent blockage of the pulmonary lymphatic vessels, it seems unusual that this complication does not occur more frequently. In none of the patients was involvement of the bony thorax noted. This may be of value in differentiating the malignant conditions with which sarcoid may be confused.

The hands and feet were examined in 27 patients. Of these, 6 had indisputable lesions in the hands and 1 was considered as having questionable changes, an average of 22 per cent with indicative signs. No lesions were found in the feet or in any of the long bones when they were examined, although they have been reported by others (Reisner⁸ and Longcope²⁸). The presence of skeletal involvement is thought to be strongly suggestive of sarcoid, and even with a low incidence of 22 per cent a routine examination of the hands in suspected cases would

53. Bernstein, S. S., and Oppenheimer, B. S.: Boeck's Sarcoid: Report of Six Cases with One Necropsy, *J. Mt. Sinai Hosp.* 9:329-343, 1942.

54. Salvesen, H. A.: The Sarcoid of Boeck: A Disease of Importance to Internal Medicine, *Acta med. Scandinav.* 86:127-151, 1935.

At necropsy the chief feature of interest were the lungs, the right lung weighing 1,750 Gm. and the left 1,510 Gm. They were exceedingly firm throughout, the pleural surface was smooth and there were no adhesions. On section, a diffuse, firm cellular infiltration of greenish gray color was seen throughout, leaving extremely little normal pulmonary tissue. This gray cut surface seemed to be composed of innumerable nodules which had coalesced. There was no cavitation or necrosis. The hilar lymph nodes, enlarged to a diameter of 5 by 3 cm., were firm and showed a greenish gray cut surface. There were gray granulomatous nodes in the liver and spleen, these organs weighing 1,740 Gm. and 240 Gm. respectively. The weight of the heart was 400 Gm., with hypertrophy, particularly of the right ventricle. The wall of the left ventricle measured 1.6 cm. and the wall of the right ventricle 1.2 cm. in thickness. There was no gross evidence of involvement of the cardiac muscle or pericardium. Microscopic study of multiple sections showed the normal pulmonary tissue almost entirely replaced by a granulomatous process. There were innumerable nodular aggregates of epithelioid cells and many multinucleated giant cells. The giant cells had a tendency to contain more nuclei and to show a somewhat different configuration from those seen in the spleen and liver. All other organs and tissues, including the brain, pituitary, thyroid, heart, pancreas, kidneys, adrenals, prostate, testicles and vertebral bone marrow, were free from the process.

CASE 3.—The patient was a 13 year old white girl who had fever, a weight loss of 25 pounds (11 Kg.) and severe anemia. She had had fever for six weeks before she was seen at the hospital in December 1944. This patient showed the most widespread involvement of various organs that we have seen. There were bilateral uveitis and keratitis, bilateral parotitis and enlargement of the submaxillary glands. Transient paralysis of the right side of the face, due to the parotid swelling, developed. Generalized lymphadenopathy and extreme anemia were found. There was involvement of the bones of the hands (fig. 11). The spleen and liver were palpable, and urinalysis repeatedly showed albuminuria, occasional red cells, many pus cells and many hyaline and granular casts. The reaction to the tuberculin test was negative. The total protein was 7.9 Gm. per hundred cubic centimeters, with globulin 3.9 Gm. The sedimentation rate was 34 mm. A roentgenogram of the chest revealed enlargement of the peribronchial and paratracheal lymph nodes, with a fine reticular infiltration of both lungs when first seen (fig. 2 A). Biopsy of the right epitrochlear node showed typical epithelioid tubercles, with giant cells characteristic of sarcoid. The patient improved considerably under general care, rest, diet and administration of vitamins and iron. When last seen, in February 1946, she was much improved, the anemia had been corrected, she had gained weight and the lymph nodes in the chest had decreased in size, leaving only strandlike markings in the lungs (fig. 2 B).

CASE 7.—The patient was a 26 year old Negro, whose complaints were fever, pains in the chest and cough. He had questionable enlargement of the cervical lymph nodes and bilateral iridocyclitis. The tuberculin patch test gave a negative reaction. He ran a febrile course throughout, the temperature reaching as high as 105 F. While he was under observation, small cutaneous nodules developed in the right leg and left forearm. Biopsy of these nodules showed changes consistent with the picture of sarcoid. There was some improvement in the eyes but no improvement in general condition, and he was transferred to a Veterans' Facility hospital for further treatment. This patient showed two features of interest. He had a decided elevation of temperature during his entire three months of observation. The second point is the fact that the cutaneous nodules were not obvious and were only found on search for a source of material for biopsy.

more frequently. It may be that in the majority of cases the lesions are too small or too diffuse to cause recognizable alterations in the osseous structures. In no instance has involvement of the joint been found except for calcification in the periarticular tissues of the metacarpophalangeal joints of 1 patient. In the case of 1 adolescent patient of 13 years of age in whose hands osseous lesions were found we wondered whether these lesions might interfere with epiphysial growth, but a follow-up study indicated that epiphysial development was proceeding normally. A longitudinal striation of the finger nails has been described in association with the osseous lesions of sarcoid (Harrell¹²), but we have not observed it.

TREATMENT

It is not the purpose of this paper to discuss the treatment of sarcoid. However, the question of treatment of intrathoracic lymphadenopathy by high voltage roentgen therapy is often raised. In 2 of our patients a test dose of 1,300 r. was given, with the use of 220 kilovolts and 15 milliamperes, a 50 cm. distance and a half-value layer of 1.34 mm. of copper. In neither of these cases was there an observable reduction in the size of the lymph nodes or an alteration of the clinical course of the disease. The value of this dose of radiation as a therapeutic test is in itself open to question. The pulmonary manifestations are known to regress spontaneously, and if this occurred simultaneously with the administration of deep radiation it might lead to an erroneous conclusion.

REPORT OF CASES

CASE 1.—It seems worth while to report in detail the only case which came to necropsy. The patient was a Negro, 26 years of age, who first noted mild shortness of breath and cough in June 1942. Because of increase in these symptoms, he was hospitalized on June 12 when a diffuse infiltration of both lungs of unknown cause was discovered. The only physical signs were slight impairment of the percussion note and medium and fine moist rales at the bases of both lungs. The paucity of signs was in striking contrast to the roentgen study of his chest, which showed nodular areas of increased density throughout all portions of both pulmonary fields (fig. 1). Roentgenograms of the hands showed the typical lesions of sarcoid (fig. 11). There was no involvement of the skin or superficial lymph nodes. The sputum was sterile on repeated culture, and smears for fungi and acid-fast bacilli were negative. The gastric washings were likewise sterile. A blood count and urinalysis were noncontributory. The total protein varied between 6.7 and 8 Gm. per hundred cubic centimeters, and the highest globulin level was 3 Gm. The sedimentation rate was 38 mm. in one hour (Wintrobe).

Ambulatory and afebrile on his admission to the hospital, the patient gradually grew worse until December 29, when he became cyanotic and dyspneic, coughed up a little blood and had a low grade fever for several days, the maximum temperature being 100.6 F. He was given sulfadiazine for about three weeks, after which he improved and the temperature became normal. From this time on he became increasingly cyanotic, and oxygen was needed most of the time until he finally died on May 29, 1943, a little less than a year from the date of his first symptoms.

confirmed by blood pressure readings. On May 5, 200 cc. of straw-colored fluid was removed from the pericardial cavity, with some relief of dyspnea (fig. 7). The blood pressure was 100 systolic and 70 diastolic before and 110 systolic and 70 diastolic after the aspiration.

There were 11,000 to 14,000 leukocytes, with a normal differential count. The temperature varied from 99 to 101 F., and the sedimentation rate was 57 mm. in one hour (Wintrobe).

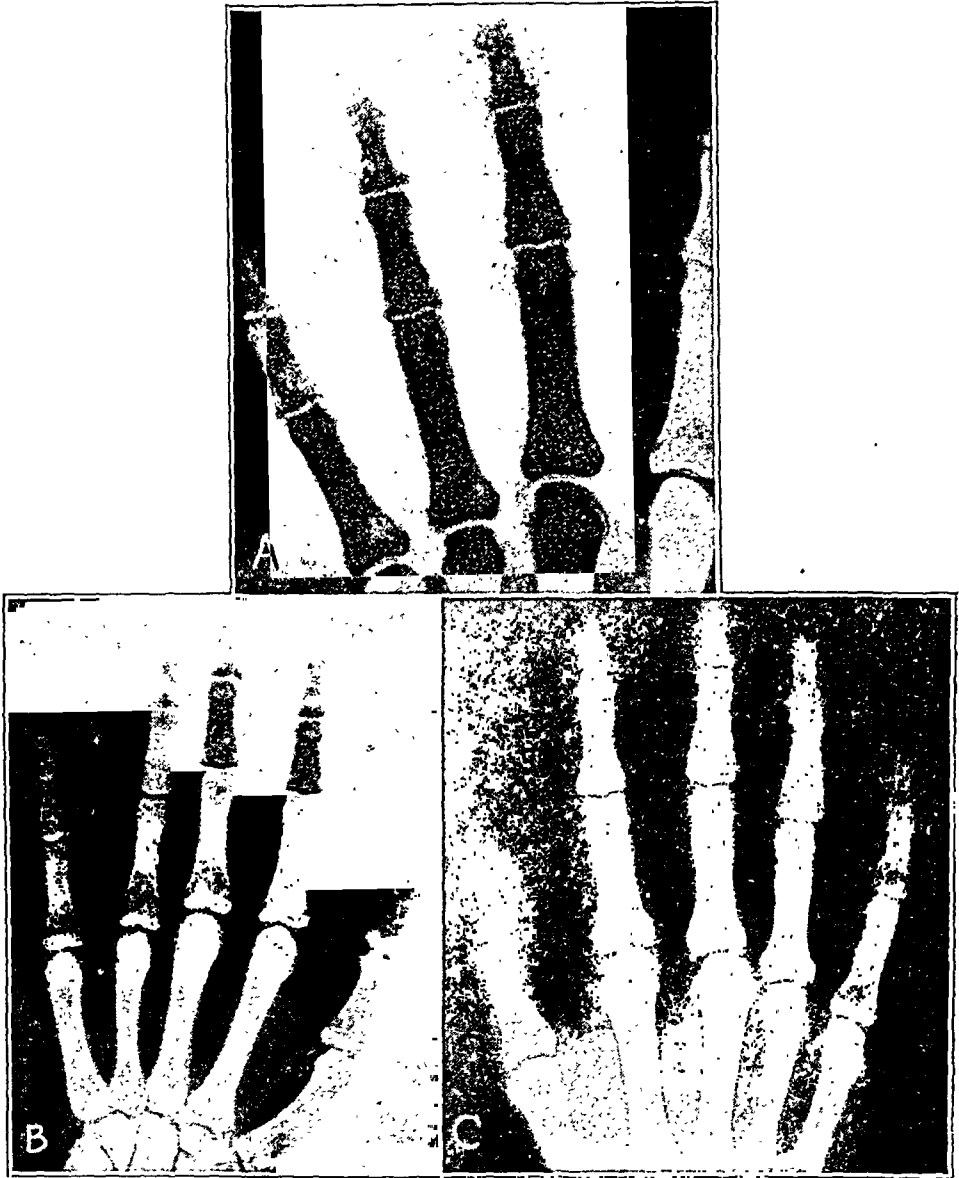


Fig. 11.—*A* (case 1), small oval areas of diminished density are noted in the distal and proximal ends of the phalanges. *B* (case 3), there is a diffuse rarefaction of the bones, with the areas of diminished density localized predominantly along the ends of the phalanges. No disturbance of epiphysial growth was noted in the hands of this adolescent patient during the period of observation. *C* (case 17), a diffuse rarefaction of the bones is seen in the hands of this patient, with occasional small oval areas of diminished density.

The patient received roentgen therapy, 1,300 r. at 220 kilovolts directed to the mediastinum, without noticeable effect. A total of 1,200 cc. of fluid was removed

CASE 9.—A 21 year old white man was injured in combat by a shell fragment, resulting in the loss of one leg and a compound fracture of the other.

On his evacuation to this hospital a roentgenogram of the chest was taken because of a chronic persistent cough. An enlargement of the paratracheal and peribronchial lymph nodes bilaterally was revealed (fig. 6A). The nodes were smooth and rounded and did not tend to be confluent. No calcifications were seen, and no compression of the trachea or bronchi was apparent. The patient stated that he had had a persistent cough of about two months' duration prior to this time. All laboratory studies were noncontributory except that on one occasion there was an eosinophil content of 11 per cent (table 2).

A small lymph node removed from the cervical chain showed most of the parenchyma replaced by rather sharply demarcated tubercles composed of epithelioid cells and occasional large multinucleated giant cells. There was necrosis in the center of some of the tubercles, but no actual caseation was encountered. Ziehl-Neelsen stain showed no acid-fast bacilli.

Over a period of nine months a gradual regression in the size of the mediastinal lymphadenopathy was noted, but simultaneously there appeared a faint strandlike

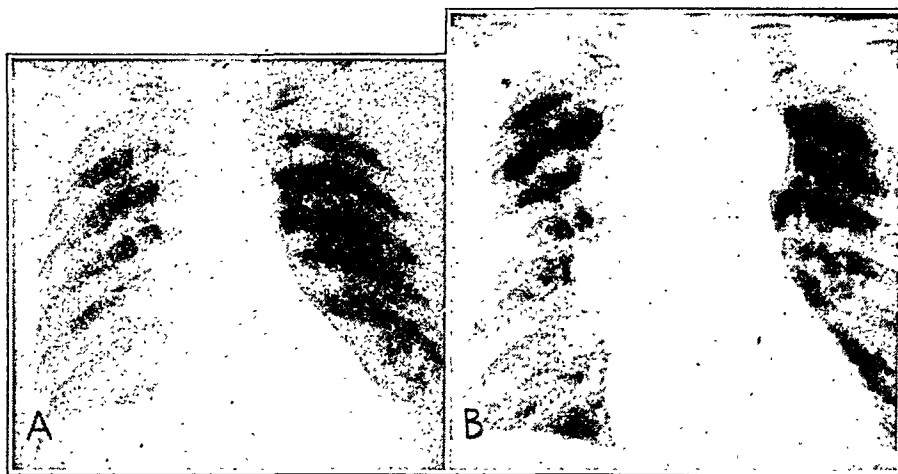


Fig. 10 (case 17).—A, on July 10, 1943, there is moderate enlargement of the peribronchial lymph nodes. The esophagus can be seen outlined by a small amount of barium. Just below the carina it shows considerable deviation, which is probably due to the enlargement of the bifurcation group of lymph nodes. B, on Feb. 1, 1946 the patient had a thoracotomy performed, and a lymph node was removed from the anterior mediastinum, which on final examination disclosed sarcoid. There has been a further enlargement of lymph nodes in the paratracheal region.

infiltration throughout both pulmonary fields (fig. 6B). During the period of observation, the patient remained in comparatively good health and had only a slight occasional cough.

CASE 10.—The patient was a 31 year old white man who while being treated in the dispensary for pain in his left knee in March 1943 complained of dyspnea on strenuous exertion. He was then noted to have generalized lymphadenopathy of the sublingual, cervical, left epitrochlear and inguinal nodes. Biopsy of a sublingual node on April 7 showed the typical pathologic appearance of sarcoid.

Later, low grade fever developed and the liver became palpable, and by May 2 he had orthopnea and a pericardial friction rub was heard. On May 3 the pulse was weak and rapid (100 to 120) and the small volume and pulsus paradoxus were

4. No instance of a false positive reaction to a serologic test for syphilis was noted.

5. The finding of a frequently negative reaction to the tuberculin test and of a high globulin value was confirmed.

6. A detailed roentgen study of the 28 cases revealed the following features: (a) enlargement of the paratracheal lymph nodes in all; (b) enlargement of the peribronchial lymph nodes in 25; (c) pulmonary parenchymal involvement in 15; (d) pleural effusion in 2 instances; (e) pericardial effusion in 1 instance, and (f) osseous changes in the hands of 6 patients.

7. In 11 of the 28 cases the enlargement of the intrathoracic lymph nodes was more prominent on the right side, which may be explained on the basis of the anatomic finding that in the normal chest the lymph nodes are more numerous on this side. This fact is of no value in the differential diagnosis of benign and malignant lymphogranuloma, as was once suspected.

8. In 27 of the 28 cases the enlarged intrathoracic lymph nodes tended to remain discrete and well defined. Calcification within the lymph nodes was seen in only 1 instance.

9. In the course of the disease the enlarged lymph nodes may undergo spontaneous regression, to be replaced by fibrous tissue; this may be accompanied with increased evidence of parenchymal pulmonary involvement.

10. There was but 1 death in this series, which was due to failure of the right side of the heart secondary to extensive infiltration of the pulmonary involvement.

11. Radiation therapy was of no value in the treatment of the enlarged lymph nodes of sarcoidosis in the 2 cases in which it was tried.

from the pericardial cavity on three occasions. Repeated cultures on this fluid failed to reveal tubercle bacilli. He showed slow but steady improvement during the autumn and winter of 1943-1944 and became asymptomatic. He secured a medical discharge from the service in February 1944. The total period of observation was eleven months.

CASE 17.—The patient was a 58 year old white man who enjoyed good health until August 1943, at which time he was found to have a mediastinal tumor (fig. 10 *A*). The tumor appeared to be due to a cluster of enlarged lymph nodes about the trachea. A thoracotomy was performed at another hospital, and one of the nodes was removed for section. The initial impression of the pathologist was that the tumor was a tuberculoma, but there were some features that suggested a Hodgkin granuloma.

In May 1945 the patient complained of weakness and dyspnea on exertion, and laboratory studies disclosed anemia of the hemolytic type, with splenomegaly. There were also hyperglobulinemia and a positive reaction to a cephalin flocculation test (3 plus). It was believed that this was a case of latent congenital hemolytic anemia, and splenectomy was performed in May 1945. The postoperative course was uneventful; however, the blood picture was not significantly altered. The pathologic changes in the spleen were consistent with the diagnosis of "hemolytic anemia," and no lesions of sarcoid were seen.

In January 1946 the patient again returned to this hospital, complaining of weakness and dyspnea. He had definite anemia, with 3,200,000 red cells and a 64 per cent hemoglobin content. There was a slight increase in fragility of the red cells. The total protein was 7.3 Gm. per hundred cubic centimeters, with albumin 4.0 Gm. and globulin 3.3 Gm. A review of the previous roentgenograms indicated that there had been an increase in the size of the lymph nodes in the paratracheal and peribronchial regions plus a strandlike infiltration in both pulmonary fields (fig. 10 *B*). The bones of the hands showed a generalized rarefaction, with several small oval areas of diminished density (fig. 11 *C*).

A review of the slides made from the lymph node removed from the anterior mediastinum two and one-half years previously showed the typical noncaseating tubercles of sarcoidosis. The anemia in this patient was not thought to be due to replacement of the bone marrow but to the formation of autohemolysins. Any relation which this formation of autohemolysin may have to sarcoidosis is conjectural.

SUMMARY

1. Of 28 proved cases of sarcoidosis, the majority of the patients were found to be young adults; 27 were men, and 15 were Negroes. This distribution is somewhat influenced by the fact that the patients were drawn from young male military personnel.

2. The symptomatology is reviewed. It is apparent that the vast majority of cases of sarcoidosis fall into four major clinical groups: (*a*) dermatologic involvement, (*b*) uveoparotid fever, (*c*) generalized lymphadenopathy and (*d*) pulmonary infiltration.

3. We were not able to confirm the incidence of leukopenia observed by other authors. Anemia was found in only 2 cases. Eosinophilia was infrequent, and the monocytes were not consistently increased.

described 2 cases in which injection of penicillin was discontinued because of severe angina, which they attributed to the drug. Callaway and his co-workers⁴ reported the probable rupture of an aortic cusp in 1 of their patients several weeks after penicillin therapy had been completed, and they attributed this to therapeutic shock. Moore¹ has reported a case of syphilitic aortitis in which the patient died in cardiac failure on the fourth day of combined malaria and penicillin therapy. The observations at necropsy in this case suggested to him the possibility of therapeutic shock. However, the evidence presented in these reports in favor of regarding any of the 4 cases as examples of Herxheimer reactions in cardiovascular syphilis is flimsy. Other investigators⁵ have not encountered serious reactions during administration of penicillin in a total of 16 patients with cardiovascular syphilis.

It is important to determine whether special precautions are indicated in this situation, not only from the standpoint of treatment of patients with recognized syphilitic cardiovascular disease but also because patients with cardiovascular syphilis are frequently given penicillin for other conditions, such as concomitant neurosyphilis, benign late syphilis or intercurrent acute infectious disease.

We have attempted to clarify this problem by presenting a preliminary estimation of the incidence and severity of untoward reactions occurring during the administration of penicillin to patients with cardiovascular syphilis.

SELECTION OF CASE MATERIAL

Between 1943 and 1947, as a part of the evaluation of penicillin therapy in late syphilis, patients with all forms of proved or suspected syphilitic heart disease were admitted to the Johns Hopkins Hospital. Cases of suspected uncomplicated syphilitic aortitis, syphilitic myocarditis or syphilitic coronary ostial stenosis were excluded from the present report because of the difficulty of establishing definitely the accuracy of the diagnosis. The data on syphilitic patients with evidences of rheumatic, severe hypertensive or arteriosclerotic heart disease were likewise omitted because it was impossible to determine clinically the relative extent of the cardiovascular damage due to syphilis. A total of 14 patients fell in these two excluded categories; no untoward reactions to penicillin were observed in them.

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PENICILLIN IN CARDIOVASCULAR SYPHILIS

Early Reactions to Administration

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A FULL evaluation of the results of penicillin therapy in cardiovascular syphilis will require observations on treated patients over a period of many years. At present, it is possible to analyze only the early reactions to administration of penicillin.

In early syphilis¹ and in neurosyphilis² the Jarisch-Herxheimer reaction ("therapeutic shock") is a frequent immediate effect of penicillin therapy. This phenomenon is of potential importance in cardiovascular syphilis because of the theoretic possibility of the occlusion of the coronary orifices or of the rupture of an aneurysm.

Moore^{1a} has advised that in the treatment of cardiovascular syphilis with penicillin "extreme caution should be exercised to avoid therapeutic shock within the first few days of treatment." This warning is based on 4 cases reported in the literature. Dolkhart and Schwemlein³

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2. (a) Reynolds, F. W.; Mohr, C. F., and Moore, J. E.: *Penicillin in the Treatment of Neurosyphilis: II. Dementia Paralytica*, J. A. M. A. **131**:1255 (Aug. 17) 1946. (b) Tucker, H. A., and Robinson, R. C. V.: *Neurosyphilitic Patients Treated with Penicillin: Probable Herxheimer Reactions*, *ibid.* **132**:281 (Oct. 5) 1946. (c) Stokes, J. H.; Steiger, H. P.; Gammon, G. D.; LaMotte, W. O.; Beerman, H.; Ingraham, N. R.; Gyorgy, P.; Rose, E. K., and Lentz, J. W.: *Three Years of Penicillin Alone in Neurosyphilis*, to be published.

3. Dolkhart, R. E., and Schwemlein, G. X.: *The Treatment of Cardiovascular Syphilis with Penicillin*, J. A. M. A. **129**:515 (Oct. 13) 1945.

these patients had symptomatic neurosyphilis with abnormalities of the cerebrospinal fluid. Two patients who had had angina at rest for over a year prior to their admission to the ward complained of typical attacks during and subsequent to administration of penicillin. One of these received a large and one a small initial dose of penicillin (table). In 10 patients on whom electrocardiograms were made before treatment from one to three tracings were taken at daily intervals after the start of therapy; in none did the records show significant change. Total and differential leukocyte counts and sedimentation rates were similarly unaffected. All patients completed therapy on schedule and without other reactions.

AORTIC ANEURYSM

The 8 patients with aortic aneurysms ranged in age from 40 to 72 years. Four were Negroes. Six were men. All had positive reactions

Early Reactions to Administration of Penicillin in Thirty Patients with Cardiovascular Syphilis

Type of Cardiovascular Syphilis	Initial Penicillin Dosage (Oxford Units)	Number of Patients Treated	Early Febrile Reactions, No. of Patients	Cardiac Symptoms During Therapy, No. of Patients	Treatment Interrupted
Aortic insufficiency.....	500 to 3,000	6	0	1	0
	25,000 to 100,000	16	4	1	0
Aortic aneurysm.....	500 to 2,000	3	1	0	0
	50,000 to 100,000	5	0	0	0
Total.....		30	5	2	0

to the serologic tests for syphilis, and in 4 the cerebrospinal fluid reacted positively to the complement fixation tests; in 1 the fluid was not examined. In each a pulsating mediastinal mass continuous with the aorta was demonstrated roentgenologically. In 2 the syphilitic origin of the aneurysm was later confirmed at autopsy. Five had cardiovascular symptoms, and 3 were in cardiac decompensation at the time of administration of penicillin. Six of seven electrocardiograms made before treatment were abnormal. One patient had received inadequate metal chemotherapy, which had been discontinued three months before his admission to the ward.

Commercial sodium penicillin in aqueous solution was given intramuscularly to 6 patients and crystalline penicillin G to the other 2. Three started with small initial doses (500 to 2,000 Oxford units), which were later increased. Four received injections of 50,000 Oxford units and the other of 100,000 units every three hours. Total dosages of penicillin ranged from 2,000,000 to 10,000,000 units.

In 1 patient who received an initial dose of 500 Oxford units there was an elevation of temperature to 100.0 F. (37.8 C.) shortly after the

There remained 22 patients with aortic insufficiency and 8 with saccular thoracic aortic aneurysm. In these patients not only could we be relatively certain of the correctness of the etiologic diagnosis but also there were clinical and/or roentgenologic evidences of syphilitic cardiovascular disease which could be evaluated objectively. Each patient was observed clinically and followed with various laboratory studies throughout the period of administration of the antibiotic.

AORTIC INSUFFICIENCY

The 22 patients with aortic insufficiency ranged in age from 37 to 68 years. Nineteen were men. Thirteen were Negroes. In 15 instances a history compatible with early syphilis was obtained. Twenty-one patients had repeated positive reactions to serologic tests, and in 16, including the patient with a negative serologic reaction, the cerebrospinal fluid reacted positively to the complement fixation tests for syphilis.⁶ The presence of aortic insufficiency was established in each patient by a definite aortic diastolic murmur and the usual peripheral signs.

At the time of administration of penicillin, 11 of the patients had cardiac symptoms. Five had dyspnea and anginal attacks of one to four years' duration, 2 had dyspnea at rest and 4 had mild exertional dyspnea for less than one year. Two were in cardiac decompensation. Eleven patients had a definite increase in the transverse diameter of the heart on roentgenologic examination. Ten of fifteen electrocardiograms made before treatment were abnormal; left axis deviation was the usual finding, but bundle branch block was noted in one and left ventricular "strain" in two records. Four patients had received metal chemotherapy after the onset of cardiac symptoms but in no instance more recently than three months prior to administration of penicillin.

Sodium penicillin in aqueous solution was given intramuscularly to 6 patients in initial doses of 500 to 3,000 Oxford units; these doses were subsequently increased gradually over a period of days until 30,000 to 100,000 units was given every three hours. Sixteen patients were placed on schedules of 25,000 to 100,000 Oxford units every three hours from the outset. Sixteen received commercial preparations of penicillin, and the others were given crystalline penicillin G; no differences were observed in the two groups. Total dosages varied from 2,000,000 to 15,000,000 Oxford units, and in no case was any other antisyphilitic drug employed.

Four of the 22 patients had elevations of temperature of from 100.0 (37.8 C.) to 102.4 F. (39.1 C.) within the first sixteen hours of treatment; all 4 received large initial doses of the antibiotic (table). All

6. The abnormally high incidence of neurosyphilis in this group was due to the fact that most of the patients were selected for admission to the ward primarily for the study of the treatment of this disease with penicillin.

sodium penicillin in aqueous solution in total dosages ranging from 2,000,000 to 15,000,000 Oxford units.

Five patients had fever (100.0 to 102.4 F.) within the first sixteen hours of treatment. Two patients with long-standing angina at rest had attacks of usual severity and frequency during and subsequent to administration of penicillin. In no instance was the treatment schedule interrupted. No significant differences in the incidence of febrile reactions or cardiovascular symptoms occurred in 9 patients receiving small initial doses (500 to 3,000 Oxford units) as compared with that in 21 patients given large initial doses (25,000 to 100,000 Oxford units) of penicillin.

Penicillin is frequently administered to patients with cardiovascular syphilis. The absence of reported severe reactions proved to be due to treatment with penicillin tends to confirm our impression that the dangers of severe untoward reactions may have been unduly emphasized. More work must be done with various dosages of penicillin in patients with cardiovascular syphilis, however, before final conclusions are justified.

NOTE.—Since this paper was submitted, 4 additional patients with cardiovascular syphilis (1 with aneurysm and 3 with aortic insufficiency) were treated with initial doses of 50,000 to 100,000 Oxford units of crystalline penicillin G. Neither febrile Herxheimer reactions nor untoward symptoms referable to the cardiovascular apparatus were noted.

start of treatment. This patient also had neurosyphilis. In none of the patients did new symptoms suggestive of a treatment reaction develop. Electrocardiograms taken on 4 of the patients during administration of penicillin revealed no change from previous records. All patients finished their penicillin schedules without incident.

COMMENT

Data on the small group of patients presented here are of limited statistical value. Undoubtedly many times this number of patients with cardiovascular syphilis have received penicillin, either as antisyphilitic therapy or as treatment for intercurrent infections. No certainly identified instances of disastrous results have appeared in the literature.

In our study 2 patients had anginal attacks at rest during treatment. Since attacks of comparable severity and frequency occurred both before and after the administration of penicillin, we do not feel that the symptoms should be interpreted as reactions to this antibiotic substance.

Only 5 of our patients had febrile reactions early in the course of injections, and each had symptomatic late neurosyphilis with notable abnormalities in the cerebrospinal fluid. The incidence of these reactions in our group of 20 patients with neurosyphilis was therefore approximately 25 per cent. In a previous study on neurosyphilis,⁴ the over-all incidence of febrile reactions during administration of penicillin was about 25 per cent. It is reasonable to assume, therefore, that the febrile reactions observed in our patients may have been related to the neurosyphilitic process rather than to the cardiovascular one. Febrile reactions occurred in none of the 10 patients without concomitant neurosyphilis.

As shown in the accompanying table, our patients fell into two dissimilar groups as regards dosage schedules. No significant differences in severity or incidence of febrile reactions or cardiac symptoms occurred in the two groups. Whereas small, gradually increasing doses of penicillin have been recommended,⁷ as has the institution of treatment with bismuth,⁸ our data fail to indicate the need for either of these expedients. Although our findings suggest that it is probably safe to treat patients with late cardiovascular syphilis with average therapeutic dosages of penicillin, final conclusions should not be drawn until many times the number of cases presented here have been carefully studied.

SUMMARY

Twenty-two patients with syphilitic aortic insufficiency and 8 with thoracic aortic aneurysm were treated by the intramuscular route with

7. Moore.^{1a} Stokes and others.^{2c} Callaway and others.⁴

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referred to the changes as fairly characteristic. Epstein and Greenspan⁸ agreed with such conclusions and failed to observe Aschoff bodies in the lungs. Coburn⁹ discussed the pulmonary consolidation of rheumatic fever as inflammatory in origin but without specific characteristics and masked by the attendant circulatory failure.

Tragerman¹⁰ reported a case of rheumatic fever with a peculiar chronic productive type of pneumonitis. Cook,¹¹ however, found the histologic appearance of the lungs to present the picture of collapse and passive hyperemia rather than that of a specific inflammatory lesion. Howard,¹² on the other hand, reviewed the subject and gave additional emphasis to the specific nature of the pleural lesions.

Hadfield¹³ agreed with Masson, Riopelle and Martin¹⁴ and described characteristic alterations in the areas of gaseous exchange. Neubuerger, Geever and Rutledge¹⁵ considered so-called Masson bodies to have a specific connotation in rheumatic pneumonitis. Herbut and Manges¹⁶ presented strong evidence against such a view.

Gouley¹⁷ emphasized the pathogenesis of the parenchymal pulmonary lesions of rheumatic fever, stressing particularly that passive hyperemia was not found to be a requisite for the development of the interstitial changes in the lungs.

Forbus¹⁸ noted the temporary consolidation termed "rheumatic pneumonia," but he stated that he had not encountered a consolidation at

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RHEUMATIC PNEUMONITIS

A Case of Widespread Chronic (Proliferative) Type with
Acute (Exudative) Foci

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CERTAIN pulmonary lesions occurring in some cases during the course of rheumatic fever and designated as rheumatic pneumonitis¹ have been the source of much interest in recent years. That fleeting and migrating pulmonary involvement occurs in rheumatic fever has been known for some time. The historical aspects of this subject were presented by Paul.² Attempts to identify the lesions by study of the tissue as one of the protean inflammatory manifestations of the rheumatic state seem to have been made only within relatively recent years.

Rabinowitz³ discussed the possibility that the fleeting pneumonopathy observed during rheumatic fever was due to the "rheumatic virus." Eiman and Gouley⁴ described lesions in the lungs of 2 patients which they considered to be similar to rheumatic cardiac lesions. Naish⁵ presented the pulmonary symptoms in 6 cases and expressed the view that the alterations observed were similar to the changes occurring elsewhere in the body during the course of rheumatic fever as described by Coombs.⁶ Fraser⁷ described "Aschoff nodules" in the lungs of patients with rheumatic fever.

Paul,² in reviewing this subject, concluded that insufficient evidence existed to support a strict specificity of the pulmonary lesions but

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1. They are also referred to as rheumatic pneumonia or pneumonopathy or the rheumatic lung.

2. Paul, J. R.: Pleural and Pulmonary Lesions of Rheumatic Fever, *Medicine* **7**:383-410, 1928.

3. Rabinowitz, M. A.: Rheumatic Pneumonia, *J. A. M. A.* **87**:142-144 (July 17) 1926.

4. Eiman, J., and Gouley, B. A.: Rheumatic Pneumonitis, *Arch. Path.* **5**:558-559 (March) 1928.

5. Naish, A. E.: The Rheumatic Lung; *Lancet* **2**:10, 1928.

6. Coombs, C. F.: The Microscopic or "Submiliary" Nodules of Active Rheumatic Carditis, *J. Path. & Bact.* **15**:489-499, 1911.

7. Fraser, A. D.: The Aschoff Nodule in Rheumatic Pneumonia, *Lancet* **1**: 70-72, 1930.

course of rheumatic fever. Lack of unanimity has existed, particularly regarding the specificity of the lesions. The theory that the lesions develop independently of the changes ascribed to passive hyperemia in textbooks on pathology²⁶ appears to have received considerable support.

The as yet controversial aspects of this subject make the case herein presented of interest, since the diffuse changes in the lungs were clearcut and associated with a classic rheumatic type of carditis. Moreover, detailed descriptions of pulmonary lesions associated with rheumatic fever are readily available,²⁷ but the cases described as displaying active rheumatic carditis and extreme and diffuse interstitial pneumonitis with advanced fibrosis ("fibro-elastosis" of Gouley) and arterial lesions are few in number. Finally, our case offers an additional point of interest in that the pulmonary lesions resemble in several respects the changes described by Hammon and Rich,²⁸ that is, acute diffuse interstitial pulmonary fibrosis not necessarily associated with rheumatic cardiac lesions.

REPORT OF A CASE

SYNOPSIS OF CLINICAL RECORD.—A 25 year old white woman was admitted to Baylor Hospital on five separate occasions during a period of sixteen months. Clinically the case was considered to be one of classic mitral stenosis with repeated bouts of congestive failure. The past history divulged an attack of "flu" at the age of 13 years, which was said to have "settled in her heart." Blindness had existed since an "eye infection" shortly after birth.

On each admission to the hospital the patient's main complaints included dyspnea, orthopnea, cough (at times productive of tenacious sputum), palpitation and on one occasion substernal pain. On the second, third and fourth admissions, in addition to congestive failure, there were bouts of fever (temperature usually 100 F. and at times 99 to 105 F. by mouth), with leukocytosis (white blood cell count 22,000, with 86 per cent polymorphonuclear cells). The febrile state was controlled with penicillin therapy (30,000 units every three hours for five to fifteen days). Digitalis preparations were used for the cardiac failure.

The laboratory findings throughout the entire time can be summarized as follows: The white blood cell count was 18,000 to 22,000, with 86 per cent neutrophils, during the febrile periods and 5,000 to 9,800, with 73 to 78 per cent neutrophils, during the afebrile intervals. The red blood cell count was 3,700,000 to 4,000,000, with a hemoglobin concentration of 8.9 to 10.4 Gm. per hundred cubic centimeters. Urinalyses showed a specific gravity of 1.008 to 1.024, an albumin content of from normal to 250 mg. per hundred cubic centimeters, few to many white blood cells and none to many red blood cells. Four blood cultures yielded no growth. The Kahn, Kline and Wassermann serologic tests

26. Karsner, H.: *Human Pathology*, ed. 6, Philadelphia, J. B. Lippincott Company, 1942. Boyd, W.: *The Pathology of Internal Diseases*, ed. 3, Philadelphia, Lea & Febiger, 1940.

27. Naish.⁵ Epstein.⁸ Hadfield.¹³ Gouley.^{17a}

28. Hammon, L., and Rich, A. R.: *Acute Diffuse Interstitial Fibrosis of the Lungs*, *Bull. Johns Hopkins Hosp.* 74:177-212, 1944.

autopsy that could be considered truly rheumatic in origin, even when acute myocarditis existed. The clinically observed phenomenon was, therefore, interpreted as the result of a mechanism "not peculiar to rheumatic fever."

More recently, Jensen¹⁹ and Griffith, Phillips and Asher²⁰ have reported on rheumatic pneumonitis. Death in Jensen's case was analyzed as being primarily due to acute pulmonary lesions. Griffith and his associates described and classified the lesions in 119 instances of pulmonary involvement in 1,046 cases of rheumatic fever (an incidence of 11.3 per cent). They interpreted rheumatic pneumonitis as an entity "only when considered as one of the manifestations of the widespread angitis of rheumatic fever."

Swift²¹ has for some time laid emphasis on the allergic aspect of rheumatic fever. Melnick²² discussed the findings at autopsies on 6 patients who died from acute rheumatic fever, and he concluded that the pulmonary "process resembles an allergic reaction." More recently, Gregory and Rich²³ have presented additional data in support of hypersensitivity in the development of the lesions of rheumatic fever. The pulmonary lesions were included in the mechanism, and great stress was given to vascular alterations. Von Glahn and Pappenheimer²⁴ earlier reported on lesions in arteries during rheumatic fever and described the sequence of changes in the arterial wall. The pulmonary arteries were involved not infrequently in their group of cases. Paul²⁵ also discussed lesions of pulmonary arteries.

Such a review of this topic, although affording an insight into differences of opinion, nevertheless demonstrates that several observers have noted the development of fairly characteristic pulmonary changes in the

19. Jensen, C. R.: Nonsuppurative Poststreptococcal (Rheumatic) Pneumonitis: Pathologic Anatomy and Clinical Differentiation from Primary Atypical Pneumonia, *Arch. Int. Med.* **77**:237-253 (March) 1946.

20. Griffith, G. C.; Phillips, A. W., and Asher, C.: Pneumonitis Occurring in Rheumatic Fever, *Am. J. M. Sc.* **212**:22-30, 1946.

21. Swift, H. F.: Rheumatic Fever; Hektoen Lecture, Billings Foundation, *J. A. M. A.* **92**:2071-2083 (June 22) 1929.

22. Melnick, P. J.: Pulmonary Changes in Rheumatic Fever, *Illinois M. J.* **73**:336-340, 1938.

23. (a) Gregory, J. E., and Rich, A. R.: Experimental Production of Anaphylactic Pulmonary Lesions with Basic Characteristics of Rheumatic Pneumonitis, *Bull. Johns Hopkins Hosp.* **78**:1-12, 1946. (b) Rich, A. R.: The Role of Hypersensitivity in the Pathogenesis of Rheumatic Fever and Periarthritis Nodosa, *Proc. Inst. Med. Chicago* **15**:270-280, 1945.

24. Von Glahn, W. C., and Pappenheimer, A. M.: Specific Lesions of Peripheral Blood Vessels in Rheumatism, *Am. J. Path.* **2**:235-249, 1926.

25. Paul, J. R.: Lesions in the Pulmonary Artery in Rheumatism, *Arch. Path.* **3**:354 (Feb.) 1927.

of the blood elicited negative reactions. No cold agglutinins were observed. Erythrocyte sedimentation rates (Cutler) were 22 to 26 mm. in one hour.

Roentgenograms of the chest revealed enlargement of the left auricle, deviation of the esophagus to the right and pulmonary congestion. After the patient's fourth admission to the hospital (May 28, 1946), a report on a roentgenogram described the presence of confluent pneumonic consolidation of the base of the right lung. The existence of "rheumatic pneumonitis" was considered at this time.

During the final stay in the hospital (June 27 to July 7, 1946), the outstanding features were remittent fever peaks of 101 F., backward heart failure and signs of consolidation in the middle and lower lobes of the right lung. A roentgenogram demonstrated patchy and confluent consolidation of the lower lobe of the same lung and bilateral pleural thickening. Cyanosis was not intense. The patient died nine days later after being in a shocklike state for a few hours.

AUTOPSY.²⁹—*Gross Findings.*—The body was that of a poorly nourished white woman 59 inches (150 cm.) in length and with an approximate weight of 100 pounds (45 Kg.). The corneas were thickened and opaque. There was an old midline scar in the lower part of the abdomen (appendectomy scar). The skin was everywhere pale.

The right pleural space had 800 cc. of dark brown fluid and the left pleural space 300 cc. There were no pleural adhesions. The pericardial space had 100 cc. of yellowish fluid, and the pericardial surfaces were smooth and glistening.

Heart: The weight of the heart was 260 Gm. The left ventricle was small and the left antrum large and dilated. The right atrium and right ventricle were moderately enlarged. The myocardium was firm and reddish brown. The circumference of the valves in centimeters was as follows: tricuspid 10, pulmonic 6, mitral 2 and aortic, 7. The mitral leaflets were adherent and thickened and formed a fixed, markedly stenosed, funnel-shaped structure; the chordae tendineae were shortened and thickened. At the near edge of the fused leaflets were minute, friable, verrucous vegetations. There was a single vegetation 3 mm. in diameter on the posterior atrial wall, 1 cm. above the posterior mitral leaflet (MacCallum patch area). The other valves were unaltered, and the remainder of the endocardium was smooth. The coronary vessels were of normal appearance.

Lungs: The weight of the right lung was 1,000 Gm. and that of the left 800 Gm.

The pleura of the right lung was thickened, especially over the lower lobe. All three lobes were firm and retained their shape well. The only area of normal crepitation was an area 5 cm. in diameter about the apex. On section the upper lobe was firm and dark red, and abundant frothy fluid could be expressed from the cut surface. The upper half of the lower lobe was of the same appearance as this. The entire middle lobe and the lower half of the lower lobe were firm and rubbery and yellowish gray, with a dry cut surface from which little air escaped.

The left lung resembled its fellow. The entire upper lobe was dark red and firm and exuded frothy fluid on section. The entire lower lobe was pale gray, firm, rubbery and dry and resembled the lower area of the right lung.

The bronchi on both sides were nearly empty and showed no dilatation. The larger blood vessels were grossly unaltered. There was no evidence of tuberculous lesions at the apex.

29. Autopsy was performed three hours after death.



Fig. 1.—Section of the lower lobe area demonstrating remnants of hyaline membranes and hemosiderin-containing macrophages in alveolar spaces. The alveolar walls are fibrously thickened and show a decrease in vascularity and scattered groups of inflammatory cells, mainly lymphoid cells and macrophages. The cuboidal lining of alveolar spaces is also pictured.

Liver: The weight was 1,330 Gm., and section showed the dark red and gray mottling of passive hyperemia.

Spleen: The spleen weighed 190 Gm. and was firm and rubbery.

Kidneys: The weight of the right kidney was 140 Gm. and that of the left 150 Gm. The appearance was normal.

Other Organs: No gross abnormalities were noted in the esophagus, stomach, gallbladder, pancreas, adrenal glands, ureters, urinary bladder, uterus, uterine tubes, ovaries and central nervous system.

*Microscopic Examination.*³⁰—Heart: Left ventricle. Prominent venocapillary hyperemia was present, with myocardial fibers of normal size. The myocardium near the epicardium was heavy with mononuclear cells (lymphoid and larger forms). There were similar cells in the connective tissue near the arterial branches plus occasional plasma cells, eosinophils and Aschoff cells (with lobulated vesicular nuclei, abundant purplish cytoplasm and ill defined borders). Some cellular accumulations were sufficiently concentrated to warrant the designation of Aschoff bodies.

Anterior mitral leaflet and aortic cusp. The mitral leaflet was thick and hyaline, and the aortic cusp was normal. Between these structures the myocardium had many dilated vessels and scattered small recent hemorrhages. The mural endocardium had many small mononuclear cells here.

Leaflet vegetation. Eosinophilic fibrin-like material with many polymorphonuclear neutrophilic leukocytes was present; the leaflet was partly calcified.

Left atrium at MacCallum patch. The connective tissue of the thickened endocardium had separated bluish granular collagen bundles. The adjoining connective tissue and the myocardium contained numerous oval and round cells of typical Anitschkow myocyte type (nuclei with central chromatin condensation and strands radiating to nuclear membrane, ill defined cytoplasm and palisade-like arrangement).

Right side. There was no significant finding here.

Lungs: Upper lobes. The pleura was of normal thickness. The parenchymal alveolar pattern was regular, but the alveolar walls were greatly thickened because of considerable capillary hyperemia and increased cellularity. The cells consisted mainly of fibroblasts, but scattered lymphoid cells, plasma cells and macrophages were also seen. The lining of many alveoli was of the cuboidal epithelium type. The smooth muscle of the terminal bronchioles was hypertrophied.

The alveolar spaces were nearly empty in some areas but were filled with protein precipitate (edema) and hemosiderin-laden macrophages in others. Occasional hemosiderin-containing giant cells were seen. Ill defined to definite hyaline membranes were seen adhering to the lining of several alveolar ducts and alveoli.

Focal areas, involving 50 to 75 per cent of microscopic fields (60 diameters magnification), demonstrated replacement of alveolar pattern by a delicate and loose connective tissue. Such areas contained young plump type fibroblasts, fine, delicate intercellular fibrils, scattered lymphocytes, plasma cells and macrophages with and without hemosiderin pigment.

Groups of intact red blood cells were seen in some alveolar spaces (capillary hemorrhages); compact hemorrhages were not present. Larger blood vessels were distended with blood, but the walls were normal in appearance.

Lower lobes. The pleura was moderately thickened, containing fairly dense fibrous tissue, scattered capillary-sized blood vessels, prominent focal accumu-

30. The stain used was hematoxylin and eosin.

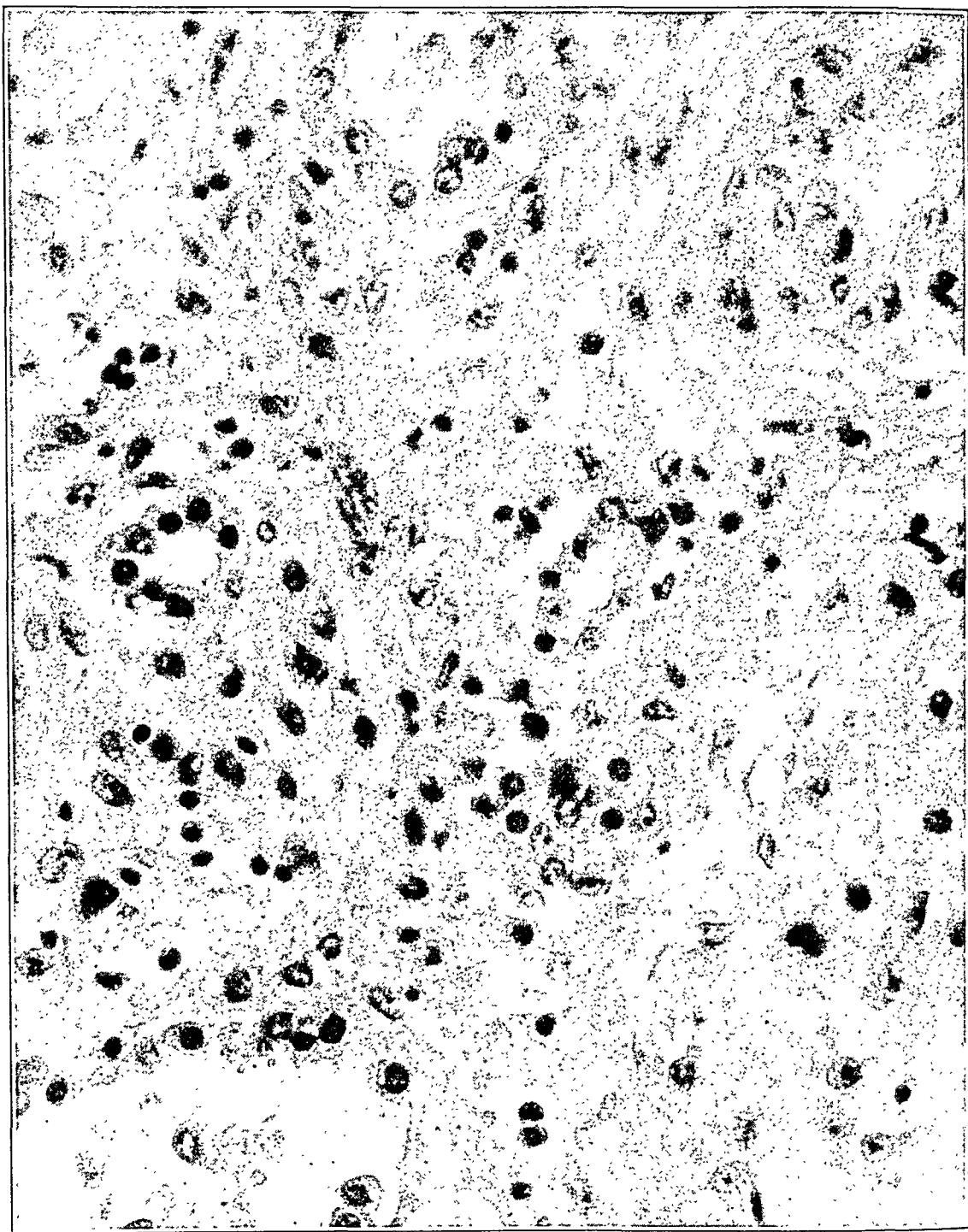


Fig. 2.—A closer observation of the thickened alveolar walls. Fibroblasts and intercellular fibers containing the mononuclear exudate are seen. Again the disturbed vascularity and the cuboidal lining of alveolar spaces can be noted.

densely arranged and intertwined intercellular fibers. There was pronounced infiltration of fibrous tissue with mononuclear cells (lymphocytes, plasma cells and macrophages). Hemosiderin-laden macrophages were present.

The number of capillaries in the alveolar walls was markedly decreased. The larger blood vessels were the seat of notable changes. There was separation of the muscle bundles of the media by loose vascular connective tissue, and the lumens were replaced by connective tissue having scattered small blood vessels

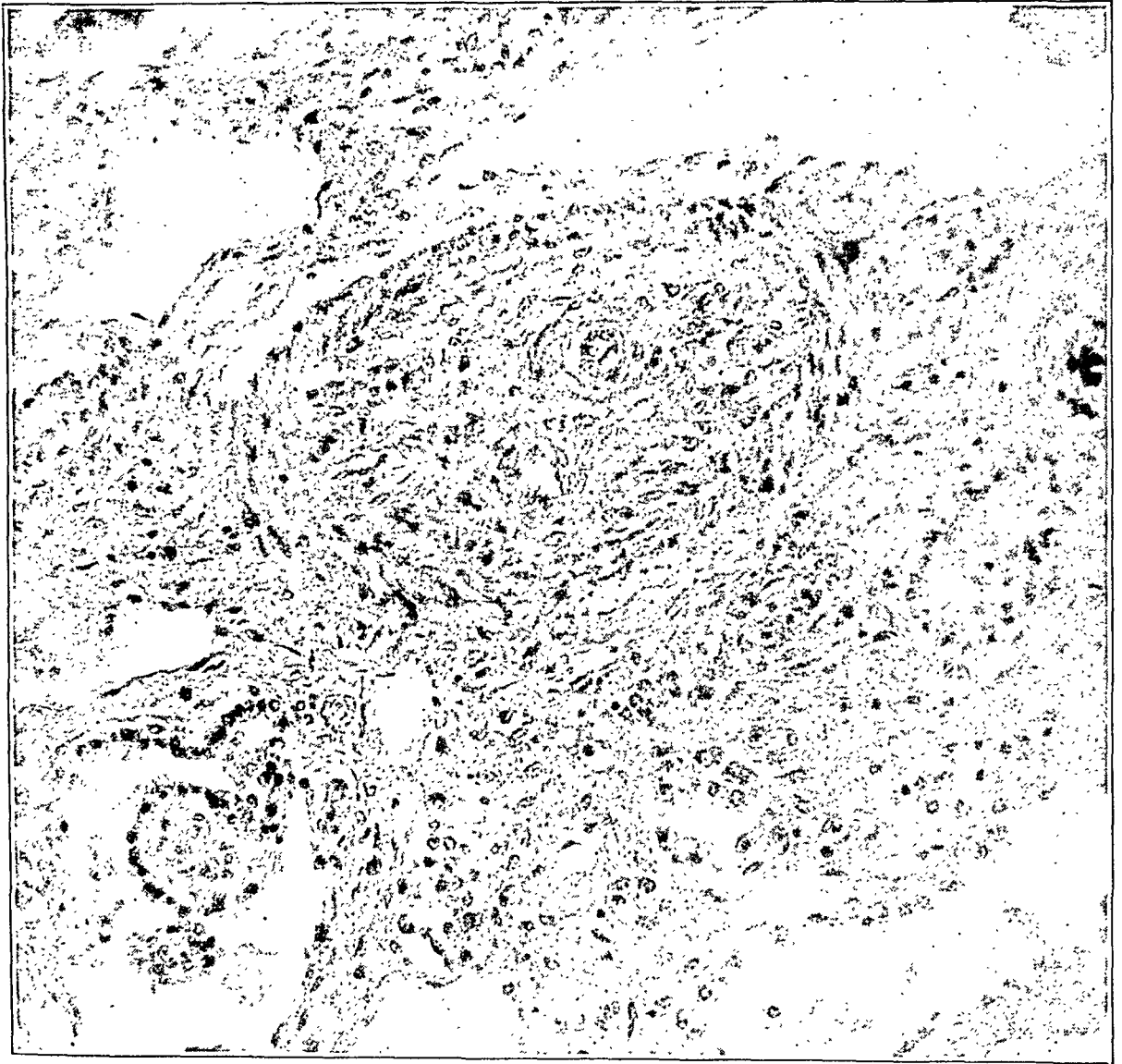


Fig. 4.—A close-up example of the healed arterial lesion is displayed. The resemblance to a canalized thrombus can be appreciated. Some portions of the muscular structure of the media have been separated by the loose type of connective tissue, while other portions remain intact. Another "Masson body" is noted in the left lower corner.

(appearance of canalized thrombi). In the loose connective tissue of the adventitia groups of round cells were seen (lymphoid and plasma cells and macrophages but no eosinophils).

The alveolar spaces either were empty or contained clusters of hemosiderin-laden macrophages. So-called Masson bodies were prominent everywhere. These

lations of inflammatory cells, mainly lymphocytes and macrophages, and a few eosinophils and plasma cells.

In the parenchyma the alveolar walls were greatly thickened and the alveolar spaces were small and lined with cuboidal epithelium. The thickening of the walls was due to abundant connective tissue having plump fibroblasts and loosely to

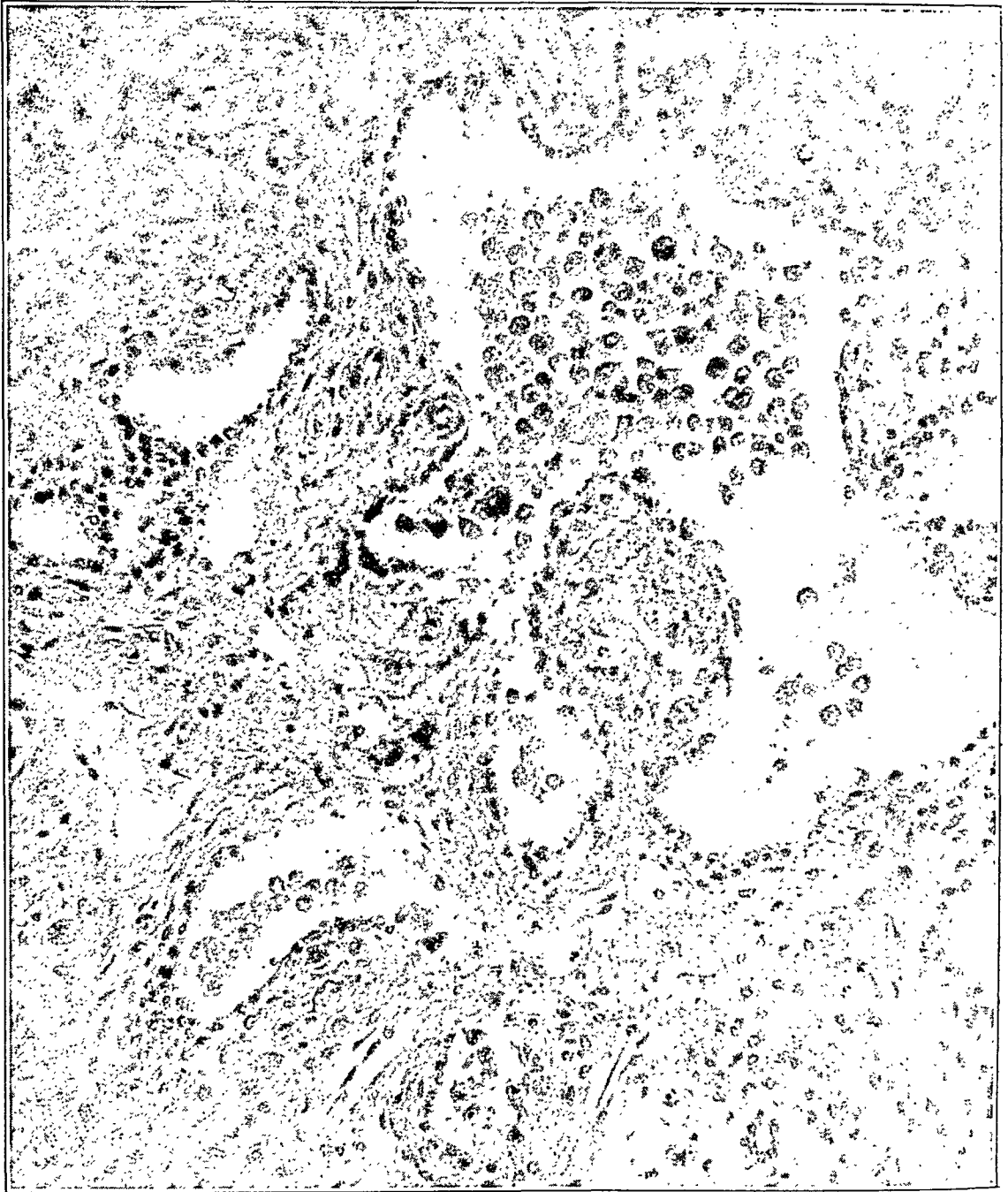


Fig. 3.—A so-called Masson body is demonstrated, being attached by means of a fibrous pedicle. The construction of these bodies is similar to that of the thickened alveolar walls. The intra-alveolar and interstitial cellular exudates can be noted to be similar.

diffuse fibrosis and partly healed arteritis; (2) chronic panvisceral passive hyperemia; (3) acute parenchymatous degeneration of the liver and kidneys; (4) focal calcification of the renal tubules, and (5) corneal opacities.

PULMONARY CHANGES IN RHEUMATIC PNEUMONITIS

Several observers have presented detailed description of the pulmonary changes in rheumatic pneumonitis. Despite some differences concerning specific aspects of the tissue response, a certain central theme can be appreciated in these various observations.

Gouley^{17a} classified rheumatic pneumonopathy into acute, subacute and chronic forms. The acute form was considered to begin in a destructive phase (foci of fibrinoid necrosis in alveolar walls, monocytic infiltration and endothelial proliferation), which then passes into a proliferative phase (infiltration of large basophilic cells called "Aschoff cells" in perivascular and interstitial spaces), followed by a reparative phase (presence of plasma cells, lymphocytes and proliferated fibroblasts, with greater elaboration, and greater amounts of collagen and destruction of elastic and reticular framework of alveolar walls). In the subacute form the reparative process continues, giving rise to early diffuse interstitial fibrosis, many macrophages and early regeneration of elastic tissue ("elastosis"). The chronic form is characterized by thick alveolar walls due to collagenous fibrosis, diminished capillary blood supply, cuboidal alveolar lining and hyperplasia of elastic tissue ("elastosis"). Grossly, the early forms are featured by a mottled appearance resembling hemorrhagic edema, irregular infarcts or definite consolidation. The later forms give rise to varying degrees of "rubberoid" appearance of the lungs.

Epstein and Greenspan⁸ described the pulmonary lesions in a related fashion. In patients who died during the initial attack of rheumatic fever the main microscopic changes included intra-alveolar and septal edema, capillary hyperemia and hemorrhages, the presence of large mononuclear cells, the formation of hyaline membranes in 50 per cent of the cases, early organization and fibrosis and occasional hyaline thrombi in arteries. Patients having had previous attacks of rheumatic fever demonstrated atelectasis, interstitial fibrosis, organization of alveolar exudate, large numbers of cells of the form found in heart failure, hypertrophy of respiratory bronchiole musculature, considerable intimal proliferation and narrowing of arteries and arterial thrombi.

Naish's⁵ 6 patients had active rheumatic lesions elsewhere in the body. Grossly, the lungs displayed prominent areas of consolidation with "solid india rubber" appearance, being tough and red. Microscopically, the changes were considered similar to those described by Coombs and included proliferation of the endothelium of the smaller

consisted of round or oval intra-alveolar masses, frequently seen to be attached to an alveolar angle by a small pedicle. The pedicle and the mass consisted of fibrous tissue of two types, either dense and compact or loose and delicate. The bodies were covered by cuboidal epithelium and infiltrated by round cells, the same as in alveolar walls.

The bronchiolar epithelial lining was folded in compressed fashion, and columnar cells had elongated hyperchromatic nuclei. Occasional remnants of hyaline membrane were seen.

Mediastinal Lymph Node: Pronounced hyperemia and polymorphonuclear neutrophilic leukocytes, plasma cells and macrophages were present in the sinuses and medullary cords (subacute lymphadenitis).

Liver: There was evidence of centrilobular hyperemia and atrophy. There was an increase in the fibrous tissue of portal areas, and lymphocytes, plasma cells and macrophages were seen.



Fig. 5.—Roentgenogram taken fifty days before the patient's death shows pulmonary congestion and patchy and confluent pneumonic consolidation in the base of the right lung. The prominent left auricle and pulmonary conus are shown in the cardiac silhouette.

Spleen: Channelization of chronic passive hyperemia was seen in the spleen.

Kidneys: Protein precipitate was present in glomerular capsular spaces in the kidneys, with parenchymatous degeneration of convoluted tubules. There was calcification of many convoluted tubules (distal?) and collecting tubules in the cortex and medulla.

Other Organs: The adrenal glands, ureters, urinary bladder, uterus, uterine tubes, ovaries and central nervous system were of normal appearance.

Diagnosis.—The diagnosis was as follows: (1) rheumatic state with (a) advanced mitral stenosis, (b) verrucous endocarditis, mitral and atrial, (c) myocarditis of healed and active types and (d) pneumonopathy with extreme

pulmonary changes is of help in establishing more firmly the rheumatic basis for such lesions. It is with the aim of pointing out this association again that the present case is reported.

By Gouley's criteria the rheumatic pneumonopathy in the case presented conforms mostly with the chronic phase. Some features (hemorrhages, proliferating fibroblasts, delicate young connective tissue, cellular exudate and hyaline membrane) in less involved areas of the upper lobes were more in keeping with the earlier phases described by Gouley. It can be considered that healed and active processes were concomitantly present, apparently extending from the lower to the upper areas of the lungs. Aschoff cells and bodies, such as are observed in the heart and as were seen within the myocardium in this case, were not encountered in the lungs.

Several factors make the diagnosis of rheumatic pneumonitis greatly dependent on definite lesions of rheumatic fever present elsewhere in the body, preferably the heart, in addition to the fairly characteristic pulmonary changes. These factors include the lack of a specific pulmonary response which can be labeled as rheumatic beyond any doubt and, naturally, the inability to demonstrate the cause within the lungs: Other conditions may initiate tissue responses within the lungs that simulate rheumatic pneumonitis. This feature became particularly apparent when we compared the microscopic appearance in our case with that in certain cases presented by Hammon and Rich²⁸ as instances of acute diffuse interstitial pulmonary fibrosis. In this connection it is of interest that Rich^{23b} has made observations pointing toward a common factor, hypersensitivity, in several types of tissue responses heretofore considered separately.

Attempts to establish the incidence of rheumatic pneumonitis have been made, a good example being the figure 11.3 per cent presented by Griffith, Phillips and Asher.²⁰ The distinct impression is gained, however, from the review presented at the outset that the incidence of cases in which the widespread chronic (proliferative) phase is displayed is not known. One does not hesitate to consider that the figure must be low, simply on the basis of the number of such cases mentioned so far in the literature. Only through more information concerning the incidence of the widespread chronic ("rubberoid") type of disease can it be possible to gain some knowledge concerning the percentage of cases in which the acute (exudative) phase passes into the extensive chronic (proliferative) phase.

SUMMARY

A case is reported which presents the concomitant occurrence of known healed and active rheumatic cardiac lesions and a peculiar interstitial and intra-alveolar pneumonitis. The pneumonitis was widespread, demonstrating a healed (proliferative) phase with extensive fibrosis and

blood vessels, fibroblastic proliferation about the capillaries, the presence of macrophages and sometimes hemorrhage.

Fraser⁷ described exudative and proliferative features not unlike those just described⁷ but reported that typical Aschoff nodules were observed in 2 cases.

Hadfield¹³ noticed the early presence of capillary hyperemia and fibrinous exudate in alveoli and alveolar ducts and emphasized the hyaline membrane. Later (after fourteen to twenty-one days) fibrosis and mononuclear infiltration became prominent. Farber and Wilson³¹ demonstrated that two main factors were operative in the production of hyaline membranes, that is, the presence of fluid matter in the air passages and notable dyspnea.

Griffith, Phillips and Asher²⁰ considered the microscopic changes to be those of anaphylactic angiitis involving larger vessels and capillaries. They mentioned the following changes: endothelial proliferation, hemorrhage, necrosis, hyalinization and perivascular infiltration of plasmocytes, giant cells, lymphocytes and "myocytes with owl-eyed nuclei" and a few neutrophils. Aschoff bodies were found freely in various stages of development and maturity.

The findings in our case are similar to those described by Tragerman.¹⁰

Von Glahn and Pappenheimer²⁴ described arterial lesions in detail. In 47 cases of rheumatic heart disease they encountered involvement of pulmonary arteries in 21.2 per cent. Usually isolated segments of vessels were involved. The early phases were described as consisting of the following changes: swollen endothelium, accumulation of fibrinous exudate in the intima and in the entire wall, necrosis of the wall, occasional small hemorrhages, a peculiar loose cellular tissue beyond the necrotic wall having fibrillar stroma and many distorted nuclei and farther out young connective tissue with many capillaries and lymphoid cells, plasma cells and occasional eosinophils. The reparative phase was characterized by proliferation of endothelial cells and invasion by granulation tissue. The inflammatory cells disappeared, and the healed stage resembled canalized thrombi.

COMMENT

Another case in which healed and active rheumatic cardiac lesions and a unique diffuse pneumonitis and arteritis were demonstrated has been presented. The pulmonary lesions conform with those described by several observers during the course of the rheumatic state and considered by them as rheumatic pneumonitis. The repeated demonstration of the association of known rheumatic cardiac lesions and such peculiar

31. Farber, S. and Wilson, J. L.: The Hyaline Membrane in the Lungs: Experimental Study, *Arch. Path.* **14**:450-460 (Oct.) 1932.

CONTAGIOUSNESS OF COCCIDIOIDOMYCOSIS

An Experimental Study

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THIS study is directed toward a reconsideration of the issue regarding the contagiousness of coccidioidomycosis. With the high incidence of infection that occurred in large numbers of troops trained in such endemic areas as southern California, parts of Texas, Arizona and New Mexico and with subsequent demobilization, numerous soldiers harboring the fungus will return to all parts of the United States.

For an accurate evaluation of contagiousness, the causative agent must be known in its various phases and the portal of entry of the causative agent must be well understood.

CAUSATIVE AGENT AND PORTAL OF ENTRY

A. *Causative Agent (Coccidioides Immitis).*—The fungus responsible for the disease has two distinct phases in its development, as follows:

1. In the animal host it is found as a refractile thick-walled spherule (fig. 1) filled with spores. The spores may be liberated by rupture of the wall of the cyst (fig. 2), whereupon each spore may go on to develop into a spherule. This cycle is continuous in vivo or limited, depending on the progression of the disease.

2. In culture the fungus produces mycelial threads and spores (chlamydospores); the latter are cylindric (fig. 3) and thus differ from the spheres just described. Rarely, chlamydospores have been found in large cavities of the lungs of human beings, and occasionally spherules have been reported in culture.¹

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1. Baker, E. E., and Mrak, E. M.: Spherule Formation in Culture by *Coccidioides Immitis*, Am. J. Trop. Med. **21**:589, 1941. Lack, A. R.: Spherule Formation and Endosporulation of Fungus *Coccidioides* in Vitro, Proc. Soc. Exper. Biol. & Med. **38**:907, 1938. MacNeal, W. J., and Taylor, R. M.: Spherule Formation in Vitro, J. M. Research **30**:261, 1914.

an active (exudative) phase. In addition, partly healed arterial lesions were observed within the lungs.

The repeated observation of rheumatic lesions in association with pneumonitis is considered significant and supports the term rheumatic pneumonitis.

A review of leading observations on this condition has been made.

NOTE.—Since this report was completed we have observed another interesting case belonging to this category. A 21 year old white man with a clearcut history of rheumatic fever and congestive failure died suddenly (pulmonary embolism). The observations at autopsy were interesting. There were cardiac lesions of rheumatic fever type (in the myocardial, pericardial and MacCallum patch areas, anterior mitral leaflet and aortic valve). There was no mitral stenosis. The right lung was one-fourth the normal size, whitish and fibrous, and the left lung was fibrous and emphysematous. The microscopic picture was as follows: diffuse fibrous thickening of alveolar walls, prominent scattering of round cells and large clusters of hemosiderin-laden macrophages. Frequent loose irregular scars in the parenchyma, containing lymphocytes, macrophages and hemosiderin pigment, were seen. No arterial lesions were noted. There were focal lesions in the liver, pancreas and adrenal glands.

In this case the rheumatic state was associated with a demonstrable widespread inflammation, most pronounced in the lungs and heart. The pneumonitis and pleuritis were widespread and of the type encountered in the first case. The absence of mitral stenosis supports strongly the interpretation early expressed by Gouley that the pulmonary changes are due to active inflammation and not necessarily to the secondary changes of passive hyperemia associated with mitral stenosis.

Dr. H. M. Winans, Chief of the Medical Service of Baylor Hospital, assisted in the preparation of this report; the clinical studies were conducted under the supervision of Dr. A. S. McGee and Dr. J. S. Bagwell.

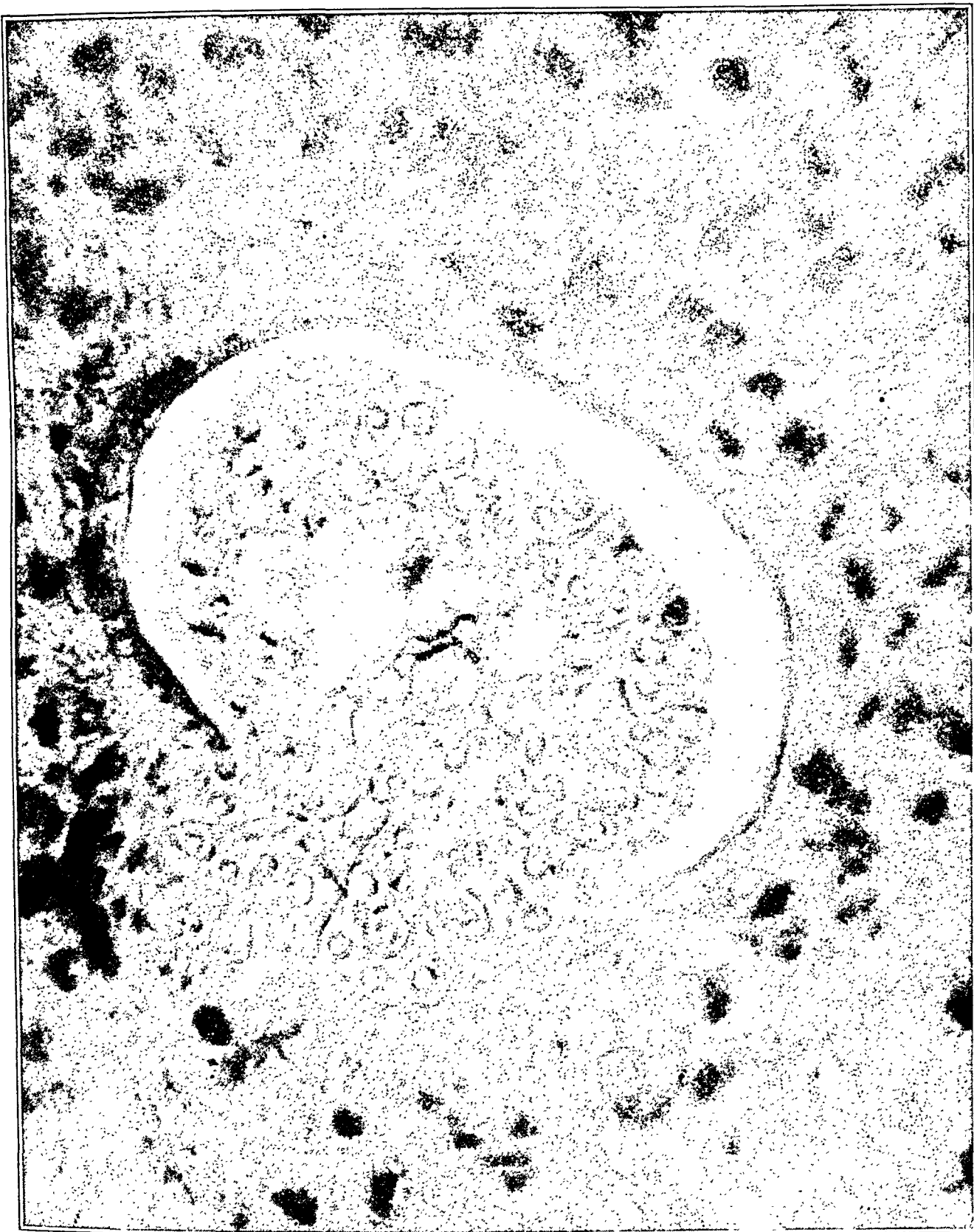


Fig. 2.—Rupture of spherule wall, with extrusion of spores. Verhoff-Van Gieson stain; $\times 758$.



Fig. 1.—Thick-walled spherule (sporangium) filled with spherical spores. Verhoeff-Van Gieson stain; $\times 786$.

The ability to culture coccidioides from the soil and the reported accidental infection in the laboratory by inhalation of chlamydospores have directed practically all animal experimentation on infectivity by the respiratory tract toward the use of cultures containing chlamydospores.⁸ That spherules when inoculated intraperitoneally, subcutaneously or intravenously do produce infection is a standard accepted fact,⁹ but infection by spherules through the respiratory tract is denied. Smith and Baker³ summarized the situation as follows:

The spherule is not adapted to dissemination of the fungus outside of the animal body. It is pointless to isolate a patient with coccidioidal infection. This great distinction to tuberculosis cannot be overemphasized. On the other hand, spores of the mycelial form are very infective. The white mycelial thread of the test tube and presumably nature from a tiny, light spore (chlamydospore), readily wafted by the breezes.

EXPERIMENTAL PROCEDURE

This study was directed into two channels: (a) the determination of whether the spherule outside of the body can remain viable for a long time without the production of mycelial threads or spores and (b) the determination of whether sputum, pus or exudate from human sources containing spherules can produce infection in guinea pigs on instillation into the respiratory tract. Judging from the literature and from personal communication with C. E. Smith, of Stanford University, a similar study has not been reported.

Source of Spherule-Containing Material.—The spherule-containing material included (1) sputum from human sources, (2) pus from human and animal sources, (3) granulation tissue from a human source and (4) lymph nodes from a human source. The lymph nodes and granulation tissue were ground in a mortar and diluted with saline solution to make a thick emulsion possible of injection through a 19 gage needle; the sputum and pus were used without dilution.

Methods of Instillation into the Trachea of Guinea Pigs.—With the guinea pig under light ether anesthesia, a 2 cm. incision of the skin was made in the midline of the neck over the trachea. The trachea was isolated by blunt dissection and was punctured with a sharp-pointed needle (20 gage). This needle was removed, and in its place a sterile, pointless, blunt needle with smooth edges that were perpendicular to the shaft needle (19 gage, 5 cm. stem) was inserted. A syringe containing exudate was attached to the needle, and 0.15 to 0.3 cc. was instilled. The syringe was removed and replaced by a clean one. About 4 cc. of air was injected, and this was repeated three to four times to propel the exudate into the finer ramifications of the respiratory tree. The syringe was removed, and then a stylet was inserted in the needle and both removed together. The wound was flooded with 70 per cent alcohol, and the skin was approximated by a silk suture.

8. (a) Ahlefeldt, F. E.: Studies in Coccidioidal Granuloma, Arch. Path. **2**:206 (Aug.) 1926. (b) Cronkite, A. E., and Lack, A. R.: Primary Pulmonary Coccidioidomycosis, J. Exper. Med. **72**:167, 1940. (c) Trager, M., and Liebow, A. A.: Intratracheal and Intraperitoneal Infection of Mouse with Coccidioides Immitis, Yale J. Biol. & Med. **15**:41, 1943.

9. Cox, A. J., and Smith, C. E.: Arrested Pulmonary Coccidioidal Granuloma, Arch. Path. **27**:717 (April) 1939. Footnotes 6 and 8 a.

Steward and Meyer,² Smith and Baker³ and Emmons⁴ have isolated the organism in coccidioidomycosis from samples of soil. It is proposed that the disease in human beings is instigated by chlamydospores, although the latter were not demonstrated in the soil; the soil may not be the source of propagation of this fungus but simply the vehicle by which the disease is spread, i. e., dust. It is generally agreed that the spherules must undergo a stage of development in nature to form chlamydospores, as seen in culture, before becoming infectious to human beings. There appears to be unanimity of opinion that there is no evidence of transmission from person to person.⁵

B. Portal of Entry.—Since the work of Ophüls,⁶ in 1905, it has been generally agreed that the usual portal of entry is the respiratory tract.⁷ Kessel^{7b} found that in 70 per cent of all cases observed at the Los Angeles General Hospital the disease originated in the lungs.



Fig. 3.—Chlamydospores in chains (ten day old culture). Note cylindric shape. Unstained; $\times 1,600$.

2. Steward, R. A., and Meyer, K. F.: Isolation of *Coccidioides Immitis* from Soil, *Proc. Soc. Exper. Biol. & Med.* **29**:937, 1932.

3. Smith, C. E., and Baker, E. E.: A Summary of the Present Status of Coccidioidal Infection, *Weekly Bull. California Dept. Pub. Health* **20**:113, 1941.

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5. (a) Dickson, E. C., and Gifford, M. A.: *Coccidioides* Infection (*Coccidioidomycosis*), *Arch. Int. Med.* **62**:853 (Nov.) 1938. (b) Stiles, G. W., and Davis, C. L.: Coccidioidal Granuloma, *J. A. M. A.* **119**:765 (July 4) 1942. (c) Meleney, H. E.: Coccidioidomycosis: Public Health Implication of Tropical and Imported Diseases, *Am. J. Pub. Health* **34**:20, 1944. (d) Smith, C. E.: Coccidioidomycosis, *M. Clin. North America* **27**:790, 1943; *Am. J. Pub. Health* **30**:600, 1940.

6. Ophüls, W.: Further Observations in a Pathogenic Mould Formerly Described as a Protozoon (*Coccidioides Immitis*), *J. Exper. Med.* **6**:443, 1905.

7. (a) Dickson, E. C.: *Coccidioides* Infection, *Arch. Int. Med.* **59**:1029 (June) 1937. (b) Kessel, J. F.: Coccidioidomycosis, *Am. J. Trop. Med.* **21**:447, 1941. (c) Stiles, G. W., and Davis, C. L.: Coccidioidal Granuloma, *J. A. M. A.* **119**:765 (July 4) 1942. Footnote 5 d.

Cultures in Guinea Pigs Subjected to Spherule-Containing Exudates

Gross Observations	Organ Examined	Postmortem Examination of Animal		Histologic Observations
		Spherules in Direct Mount in 10% NaOH †	Culture on 3% Tryptose Agar †	
Upper lobe of right lung; middle lobes; no metastasis	Operation site	+	+	Specific granuloma with spherules
	Lung	+	+	Specific granuloma with spherules
	Lymph node	—	—	Specific granuloma with spherules
Apex of left lung; miliary involvement of lung, liver, kidney and spleen	Operation site	+	+	Specific granuloma with spherules
	Lung	+	+	Specific granuloma with spherules
	Lymph node	—	—	Specific granuloma with spherules
All lobes; no metastasis	Operation site	+	+	0
	Lung	+	+	Specific granuloma
	Lymph node	—	—	Nonspecific reaction
Apexes of upper lobes and lower lobe of left lung; no metastasis	Operation site	—	—	—
	Lung	0	0	Specific granuloma
	Lymph node	—	+	Nonspecific reaction
All lobes; no metastasis	Operation site	+	+	0
	Lung	+	+	Specific granuloma
	Lymph node	+	+	Nonspecific reaction
All lobes; no metastasis	Operation site	—	0	—
	Lung	+	+	Specific granuloma
	Lymph node	0	0	0
All lobes; no metastasis	Operation site	0	0	—
	Lung	+	+	Specific granuloma
	Lymph node	0	+	Nonspecific reaction
All lobes; no metastasis	Operation site	—	—	—
	Lung	0	0	Specific granuloma
	Lymph node	0	0	Nonspecific reaction
Both lobes of left lung; no metastasis	Operation site	—	—	—
	Lung	+	+	Specific granuloma
	Lymph node	—	—	Nonspecific reaction
Apexes of upper lobes; no metastasis	Operation site	+	—	0
	Lung	+	+	Specific granuloma
	Lymph node	—	—	Nonspecific reaction
Two lobes (subapical) no metastasis	Operation site	+	+	Specific granuloma
	Lung	+	0	Specific granuloma with spherules
	Lymph node	—	0	Nonspecific reaction
Three lobes; both apexes; lesion in spleen	Operation site	+	—	Specific granuloma
	Lung	0	+	Specific granuloma
	Lymph node	0	+	0
Middle lobe of right lung; no metastasis	Operation site	+	+	Specific granuloma with spherules
	Lung	0	0	Nonspecific reaction
	Lymph node	+	0	Nonspecific reaction
Single nodule; no metastasis	Operation site	—	—	—
	Lung	+	0	Specific granuloma
	Lymph node	—	—	Nonspecific reaction

Results of Skin Tests, Gross and Microscopic Lesions and Smears and

Animal Number	Source and Age of Material	Method of Inoculation	Coccidioidin Skin Test			Days Since Inoculation
			Days	Dilution	Results*†	
3.....	Pus, 1 day (human)	Intratracheal	0	0	0	11 (killed)
6.....	Pus, 1 day (human)	Intratracheal	0	0	0	24 (killed)
7.....	Pus, 1 day (human)	Intratracheal	32	1:10 Concentrated	10x15 + + 30x30 ++ ++	67 (killed)
15.....	Pus, 19 days (human)	Intratracheal	0	0	0	8 (killed)
16.....	Pus, 19 days (human)	Intratracheal	13	1:10 Concentrated	— 8x8 Tr. Tr.	21 (killed)
17.....	Pus, 19 days (human)	Intratracheal	13	1:10 Concentrated	— 5x8 Tr. Tr.	22 (died)
19.....	Pus, 19 days (human)	Intratracheal	13	1:10 Concentrated	5x5 Tr. Tr. 10x15 + +	48 (died)
18.....	Pus, 19 days (human)	Intratracheal	13 100 160	Concentrated 1:10 Concentrated	5x5 Tr. Tr. 10x15 + +	165 (killed)
14.....	Pus, 6 days (animal)	Intratracheal	13	1:10 Concentrated	5x5 Tr. Tr. 15x20 + +	15 (killed)
13.....	Pus, 6 days (animal)	Intratracheal	13	1:10 Concentrated	10x10 — Tr. 15x15 + +	65
1.....	Granulation tissue, 1 day (human)	Intratracheal	0	0	0	9 (killed)
2.....	Granulation tissue, 1 day (human)	Intratracheal	0	0	0	11 (killed)
8.....	Granulation tissue, 1 day (human)	Intratracheal	32	1:10 Concentrated	8x8 Tr. Tr. 20x15 + ++	34 (killed)
22.....	Granulation tissue, 110 days (human)	Intratracheal	5	1:10	—	7 (killed)

Cultures in Guinea Pigs Subjected to Spherule-Containing Exudates—Continued

Gross Observations	Postmortem Examination of Animal			Histologic Observations
	Organ Examined	Spherules in Direct Mount in 10% NaOH †	Culture on 3% Tryptose Agar †	
0	Operation site	0	0	0
	Lung	—	+	0
	Lymph node	—	—	0
Four lobes; no metastasis	Operation site	—	0	—
	Lung	0	+	Specific granuloma
	Lymph node	0	0	Nonspecific reaction
Two lobes of left lung (upper and middle); no metastasis	Operation site	—	+	0
	Lung	—	—	Pneumonia; no spherules
	Lymph node	+	+	Nonspecific reaction
Two upper lobes; no metastasis	Operation site	—	—	0
	Lung	—	+	Interstitial pneumonia; no spherules
	Lymph node	+?	—	Nonspecific reaction
One upper lobe; no metastasis	Operation site	0	0	No lesion
	Lung	—	—	Interstitial pneumonia; no spherules
	Lymph node	—	—	Nonspecific reaction
Two upper lobes; no metastasis	Operation site	0	0	0
	Lung	—	+	Interstitial pneumonia; no spherules
	Lymph node	+	0	Nonspecific reaction
Two upper lobes; no metastasis	Operation site	0	0	0
	Lung	—	—	Interstitial pneumonia; no spherules
	Lymph node	—	—	Nonspecific reaction
All lobes	Operation site	—	+	0
	Lung	—	—	Granuloma; no spherules
	Lymph node	—	+	Nonspecific reaction
Two lobes of left lung; metastasis to spleen; no spherules	Operation site	+	+	Specific granuloma
	Lung	+	+	Specific granuloma
	Lymph node	+	+	Specific granuloma
Two lobes of left lung; metastasis to spleen; no spherules	Operation site	+	+	Specific granuloma
	Lung	+	+	Specific granuloma
	Lymph node	+	+	Specific granuloma
Three lobes of right lung; no metastasis	Operation site	+	+	Specific granuloma
	Lung	+	+	Specific granuloma
	Lymph node	—	—	Nonspecific reaction
No lesions; no metastasis	Operation site	0	0	No lesion
	Lung	0	0	No lesion
	Lymph node	0	0	No lesion
Millary to lung, liver, spleen and heart	Peritoneum	+	+	0
	Mesenteric	+	+	Specific granuloma
	Lymph node			
Millary to lung, liver, spleen and testicle	Peritoneum	+	+	0
	Testicle	+	+	Specific granuloma
	Meninges	0	—	0
Subpleural nodule; no metastasis	Lung	0	0	Specific granuloma; no spherules
	Lymph node	0	0	Nonspecific reaction

Results of Skin Tests, Gross and Microscopic Lesions and Smears and

Animal Number	Source and Age of Material	Method of Inoculation	Coccidioidin Skin Test			Days Since Inoculation
			Days	Dilution	Results*†	
21.....	Granulation tissue, 110 days (human)	Intratracheal	5 13 19	1:10 1:10 1:10	— — —	22 (died)
20.....	Granulation tissue, 110 days (human)	Intratracheal	25 39 70	1:10 1:10	— 8x8 + + 10x15 + +	72 (killed)
24.....	Sputum, 3 days (human)	Intratracheal	21	Concentrated	—	21 (killed)
25.....	Sputum, 3 days (human)	Intratracheal	21	Concentrated	—	21 (killed)
26.....	Sputum, 3 days (human)	Intratracheal	21	Concentrated	—	21 (killed)
27.....	Sputum, 3 days (human)	Intratracheal	21	Concentrated	—	21 (killed)
28.....	Sputum, 3 days (human)	Intratracheal	21	Concentrated	—	21 (killed)
29.....	Sputum, 3 days (human)	Intratracheal	21	Concentrated	—	28 (died)
4.....	Lymph node, 1 day (human)	Intratracheal	0	0	0	14 (died)
5.....	Lymph node, 1 day (human)	Intratracheal	0	0	0	14 (died)
9.....	Lymph node, 1 day (human)	Intratracheal	0	0	0	24 (killed)
23.....	Lymph node, 110 days (human)	Intratracheal	13 40	1:10 1:10	— 8x10 + +	72 (killed)
10.....	Pus, 1 day (human)	Intraperitoneal	0	0	0	18 (died)
11.....	Granulation tissue, 1 day (human)	Intraperitoneal	0	0	0	28 (died)
12.....	Lymph node, 1 day (human)	Intraperitoneal	32 180	1:10 Concentrated Concentrated	8x8 Tr. Tr. 18x20 ++ ++ 20x30 ++ ++	181 (killed)

* Numbers signify millimeters, and Tr. means trace to 4 plus; top reading indicates redness and bottom reading, induration.
† + indicates a positive reaction; — a negative reaction, and 0, not done.

Microscopic Examination: Lung: The lesions were those of bronchopneumonia and interstitial pneumonia (fig. 5). The exudate in the alveoli varied from fibrin and pus cells to sheets of swollen epithelioid cells. Spherules in every stage of development were noted in the exudate. In the 6 animals into which sputum was instilled, only ghosts of spherules were noted. The interstitial reaction consisted mainly of swollen histiocytes, fibrin and spherules. When the spherule's external membrane was interrupted, pus cells appeared. Giant cells were common and usually were of the foreign body type. These cells frequently contained one or more spherules or spores and seemed to be the centers for epithelioid cell granulomas. Rarely, small abscesses were noted, in which degenerated pus cells occupied the center.



Fig. 4.—Pneumonic lesion of portions of upper and lower lobes of the right lung following intratracheal instillation of spherule-containing exudate in the guinea pig. Note enlarged hilar lymph nodes.

Hilus and Paratracheal Lymph Nodes: The most common finding was wide marginal sinuses filled with swollen histiocytes, pus cells and round cells. The follicles were prominent and had large germinal centers. Occasionally granulomas composed of epithelioid cells with central necrosis or pus cells were noted in the marginal sinuses, extending into the cortex and medulla. Only rarely were spherules seen in these granulomas. At times a spherule could be found, with capsule intact, contained within a swollen giant cell or epithelial cell, without any other reaction. In less than one third of the cases spherules were noted in the nodes, although the pulmonary involvement was constant and usually extensive.

Spleen: Discrete nodules of central necrosis or pus cells surrounded by epithelial cells were occasionally noted; spherules were rare. With improvement of technic, in animals in which no lesions were noted at the site of operation the spleen remained free of involvement.

Twenty-six guinea pigs were used for intratracheal instillation and 3 for intraperitoneal inoculation. The skin of the animals was tested with a 1:10 dilution of coccidioidin (0.1 cc.) at the onset of the experiment, and it was retested at varying intervals during the experiment with 1:10 and concentrated dilutions. The animals were killed at intervals of eight to one hundred and sixty-five days (7 animals died fourteen to sixty-five days after the onset of the experiment). At autopsy, emulsions of material from the lungs, regional lymph nodes and site of injection were digested in 10 per cent sodium hydroxide and examined microscopically; cultures were made of material from the lungs, regional lymph nodes and site of injection on 3 per cent tryptose agar plates. Sections were taken of the lungs, draining lymph nodes, liver, spleen, kidneys, site of operation and cervical lymph nodes and stained with hematoxylin and eosin.

Method of Aging Spherule-Containing Exudates.—All materials were placed in test tubes and kept refrigerated at 12 C. There was frequent exposure to light, as the refrigerators were opened at numerous times during the day. At varying intervals up to one hundred and ten days direct mounts in 10 per cent sodium hydroxide, culture on 3 per cent tryptose agar plates and instillations into guinea pigs were done. Into 9 animals were instilled one day old, into 5 nineteen day old and into 4 one hundred and ten day old pus, granulation tissue and lymph node emulsions from a human source. Two animals received one day old pus from an infected guinea pig. Into 6 animals were instilled one day old sputum, and 3 animals received intraperitoneal injections of two day old pus from a human source.

In other experiments now in progress,¹⁰ spherule-containing sputum is being exposed out-of-doors in the sun and in the shade, with and without soil.

RESULTS

A. Lesions Produced After Intratracheal Instillations of Spherule-Containing Exudate.—The table summarizes the results in the 26 animals; the lesions produced in the lungs varied from well defined but irregular nodules 2 to 3 mm. in diameter to involvement of a portion or of an entire lobe (fig. 4). On section these areas were grayish white, with well defined borders and granular surfaces. Occasionally there was a small yellow fleck resembling pus in the center of some of these nodules. One or two lobes were usually involved, but in some instances all lobes were included. In practically every instance the upper lobes contained lesions. Less frequently the lower lobes were involved. The regional lymph nodes in the hilus and paratracheal regions were uniformly enlarged up to 1 to 3 cm. in diameter. On section the lymph nodes were uniformly gray to pinkish gray, with grayer zones in the cortices. The spleen was usually enlarged. Gross lesions were not seen in the liver, spleen or kidneys. In the first group of animals, before the technic was perfected, localized abscesses or zones of induration were found in the neck at the site of operation. With improvement of technic, no local lesions were noted.

10. Rosenthal, S. R., and Elmore, F. H.: Fate of Spherules in Nature, to be published.

Liver and Kidneys: Specific granulomas were found in only 1 case. They resembled specifically granulomas of the spleen. The animal involved had a local cervical lesion with many spherules.

B. *Results in Animals Inoculated Intraperitoneally.*—In contrast to those inoculated intratracheally, of the 3 animals given intraperitoneal injections the 2 killed at eighteen and twenty days presented extensive miliary involvement of the liver, spleen, kidneys, lungs and myocardium. Spherules were found in large numbers in all organs. The pulmonary lesions were pinpoint to pinhead in size and discrete. Histologically, they were perivascular, well defined granulomas with epithelioid cells, giant cells and occasional pus cells. The bronchi were free. One animal, killed after one hundred and eighty-four days, presented a single small subpleural nodule, which on microscopic examination resembled a specific granuloma without spherules. The other organs were free from involvement.

C. *Results of Aging Spherule-Containing Exudates.*—Direct mounts in 10 per cent sodium hydroxide and cultures on tryptose agar of the spherule-containing exudates kept in the cold at varying intervals from one to one hundred and ten days revealed spherules at all times. No hyphae or chlamydo spores were noted at any time. The spherules appeared plasmolyzed or distorted; yet cultures yielded few colonies after a long period of incubation.

In the sputum exposed out-of-doors, both spherules and typical hyphae producing chlamydo spores were observed in a fair percentage of the 60 specimens examined. The completed data are as yet not available.

In the group of 17 animals in which one to nineteen day old material was used direct examination of the emulsion of the material from the lungs of 13 yielded spherules in all. Of the 16 pulmonary cultures, 11 were positive. The draining lymph nodes on direct examination yielded spherules in 4 of 13 animals; 6 cultures were positive. Because of a misunderstanding, in the 6 animals into which sputum was instilled examinations were not made until three days after autopsy. In 4 of the 6 animals, nevertheless, culture of material from the lungs or lymph nodes gave positive results. Of the 4 animals inoculated with one hundred and ten day old material, typical granulomas resulted in 2. Cultures of material from the lungs of these 2 animals yielded spherules. Cultures of material from the animals killed at one hundred and sixty-five days (intratracheal group) and one hundred and eighty-five days (intraperitoneal group) were sterile.

COMMENT

The results indicate that spherule-containing pus, sputum, granulation tissue and lymph node emulsions of material from human sources when instilled into the trachea of animals produce localized and diffuse



Fig. 5.—Microscopic section of entire lobe of guinea pig, showing primary focal pneumonia following intratracheal instillation of spherule-containing exudate. $\times 14$.

2. By instilling spherule-containing sputum or exudates from human or animal sources into the bronchi of guinea pigs and propelling them by air pressure into the finer ramifications of the bronchioles and alveoli, it is possible to produce coccidioidomycosis in 100 per cent of the animals.

3. The lesions are localized for the most part in the upper portions of the lungs, are single or multiple, have a lymph node component and are not generalized, thus simulating the human infection.

4. These experiments show that spherules (or sporangia) can be infective through the respiratory route from man to animal and from animal to animal.

5. It is concluded that active primary or progressive coccidioidomycosis in human beings should be considered contagious until proved otherwise.

lesions of the lungs, with the corresponding lymph node component. Involvement in animals resembles closely that in human beings in that it is localized in the lungs, especially the upper lobes, has a corresponding involvement of the lymph nodes and is rarely generalized. Passage from animal to animal by the intratracheal route was also accomplished. Spherule-containing exudates under certain conditions will retain viable spherules without producing hyphae and chlamydospores.

It cannot be denied that infectivity of coccidioidomycosis is brought about in a large measure from other than human contact. The fact that 10 per cent of the entire Western Flying Command established in remote centers of the Southwest gave positive reactions to skin tests with coccidioidin and that in some stations 80 per cent of the population reacted positively (when in residence longer than six months¹¹) is indeed convincing evidence. The rodent reservoir suggested by Emmons⁴ warrants serious consideration. However, these findings do not exclude the possibility of contagiousness. In the past, writers failed to observe person to person contagion because only the generalized form of coccidioidomycosis was recognized. Coccidioidomycosis granuloma is a rare disease, as only 450 cases were reported in California up to July 1936. When Dickson^{7a} in 1937 pointed out that a number of respiratory diseases, diagnosed as "valley fever" or "desert rheumatism" or under other names were also caused by *C. immitis*, the widespread and endemic nature of the disease was first realized. The noncontagious view is still accepted, albeit the evidence presented in the literature is meager.¹²

Preliminary studies indicate that hyphae and chlamydospores may form in outdoor exposure of sputums, with or without soil. Thus both types of spores may be implicated as sources of infection. The respiratory tree is susceptible to the spherule as well as to the chlamydospore. The foregoing facts point to the contagiousness as well as to the infectivity of coccidioidomycosis. Although more positive evidence of transmission from patient to patient and animal to animal is necessary, until proved otherwise the disease should be considered contagious.

SUMMARY

1. The spherules of *C. immitis* remain viable under certain conditions and do not produce hyphae and chlamydospores in exudates from human sources for at least one hundred and ten days (experiments still in progress).

11. Lee, R. V.: Coccidioidomycosis in the Western Flying Command, California & West. Med. **61**:133, 1944.

12. Jacobson, H. D.: Coccidioidal Granuloma, California & West. Med. **29**:392, 1928. Smith, C. E.: Personal communication to the author; footnote 5 *d*.

members of the family were inaccessible for roentgen examination. The persons represented in cases 19, 20, 21, 22 and 23 cannot be considered in this study since no information could be secured.

Roentgenographic studies were conducted by Dr. Murray C. Goodrich, of the x-ray department of the Toledo Hospital. For each of the adults studies were made of the pelvis, the lower extremities, one pectoral girdle and one humerus. For the children studies were made of the entire body.

CASE 1.—The patient, a man, died when 53 years of age, after having twenty-seven fractures. Most of the fractures were incurred in childhood. He had severe kyphoscoliosis and lateral bowing of the femurs.

CASE 2.—A 73 year old woman had had four fractures of the left femur during her childhood. She was deaf and had been so for many years. Her scleras were

Age and Sex Distribution of the Various Manifestations of Osteogenesis Imperfecta

Case	Age	No. of Fractures		Blue Scleras		Deafness		Exophthalmos		Height	Weight, Lb.
		M.*	F.*	M.	F.	M.	F.	M.	F.		
1	53 yr.	27	4' 8"	..
2	73 yr.	..	4	..	1	..	1	5'	124
3	51 yr.	1	1	5' 2"	130
4	54 yr.	4	..	1	5' 3"	150
5	3 days	2
6	29 yr.	1	1	4' 11"	97
7	26 yr.	..	7	..	1	..	1	..	1	4' 3"	90
8	27 yr.	1	1	5' 7"	130
9	25 yr.	..	2	..	1	..	1	..	1	5' 2"	109
10	19 yr.	..	4	..	1	5' 4"	117
11	21 yr.	5' 6"	122
12	23 yr.	5' 2"	108
13	6 yr.	10	..	1	1
14	3 yr.	..	3	..	1	1
15	3 mo.	1	1
16	5 yr.
17	3 yr.
Totals.....		43	20	3	8	..	3	2	6		

* M. indicates males and F. females.

blue, as were her tympanic membranes. Roentgenograms of the pelvis and long bones revealed a large amount of callus in the upper third of the left femur. There was no lateral bowing. Many cystic areas gave it a honeycombed appearance. The femoral epiphysis was wide and also had a honeycombed appearance.

CASE 3.—With the exception of blue scleras and exophthalmos, the 51 year old woman in this case had none of the characteristic findings of osteogenesis imperfecta.

CASE 4.—The patient, a 54 year old man, had blue scleras. When he was a child he fractured his left femur three times and his right humerus once.

CASE 5.—The patient in this case was a boy born with severe kyphoscoliosis and bilateral clavicular fractures; he lived only three days.

CASE 6.—A 29 year old woman had blue scleras and pronounced exophthalmos but had had no fractures.

CASE 7.—A 26 year old woman had had seven fractures, two of the left femur and five of the right femur. All of these fractures followed slight trauma. When the patient was 11 years old she had a parathyroidectomy as well as a partial thyroidectomy, and since that time she had had only one fracture. Whether the

OSTEOGENESIS IMPERFECTA

A Study of Five Generations

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THE PURPOSE of this paper is to report a family in which five generations have been affected with osteogenesis imperfecta. Riesenman and Yater,¹ after a study of seven families, concluded that osteogenesis imperfecta (fragilitas osseum, Lobstein's disease or Vrolik's disease) is "a hereditary and familial disease and is transmitted as a dominant mendelian factor. It is a hereditary mesenchymal hypoplasia due to a disturbance of the gene or genes that determine normal mesenchymal development."

Lobstein is generally given credit for first describing this disease, but Riesenman and Yater¹ ascribed the first description to Elman in 1788. Lobstein's syndrome today is called osteogenesis imperfecta tarda in contradistinction to the syndrome described by Vrolik in 1849. The latter, at present, is referred to as the early or congenital form. Spurway² in 1896 called attention to the fact that certain patients with fragile bones also had blue scleras. Bronson³ in 1917 noted familial deafness in persons with brittle bones and blue scleras. In 1926 Key⁴ added hypertonicity of the ligaments and hypermotility of the joints to complete the clinical picture of osteogenesis imperfecta. The family studies under consideration show a high incidence of exophthalmos. The decision as to whether this feature is also part of the syndrome or whether the trait is peculiar to the family studies must await further reports.

REPORT OF CASES

The family was of French ancestry and was composed of frail, small-statured persons. The largest was 5 feet 7 inches (170 cm.) tall. All the patients represented in cases 2 to 9 and 13 to 15 inclusive were examined by me, and information on other members of the family was furnished by patients seen personally. Some

From the Department of Medicine, Toledo Hospital.

1. Riesenman, F. R., and Yater, W. M.: Osteogenesis Imperfecta, Arch. Int. Med. **67**:950 (May) 1941.

2. Spurway, J.: Hereditary Tendency to Fractures, Brit. M. J. **2**:844, 1896.

3. Bronson, E.: On Fragilitas Osseum and Its Association with Blue Sclerotics and Otosclerosis, Edinburgh M. J. **18**:240, 1917.

4. Key, J. A.: Brittle Bones and Blue Sclerae, Arch. Surg. **13**:523 (Oct.) 1926.

Laboratory Data.—The red blood cell count was 4,480,000, with a hemoglobin content of 13.2 Gm. per hundred cubic centimeters, and the white blood cell count was 9,400, with a normal differential count. The daily specimens of urine gave a 3 to 4 plus Sulkowitch reaction for calcium. The serum calcium was 10.2 mg. per hundred cubic centimeters on one occasion and 9.7 mg. on another. The serum phosphorus was 5.6 mg. per hundred cubic centimeters on one occasion and 6.0 mg. on another. The alkaline phosphatase was 7.3 and 9.8 Bodansky units on two occasions.



Fig. 2.—Representative roentgenograms in cases 2, 7, 13 and 14. *A* (case 7) shows pronounced changes, with lateral bowing, honeycombed areas of Fairbanks, thin cortices, generalized decalcification of the bones and lateral displacement of the medullary cavities. *B* (case 13) shows lateral bowing of both femurs following multiple fractures as well as the changes seen in case 7. *C* (case 2) shows generalized decalcification of the long bones, with a large amount of callus in the upper third of the left femur. *D* (case 14) is a roentgenogram of the lower extremities taken before the fracture, showing decreased density of bones and slight lateral bowing of the femurs.

Course in the Hospital.—The left femur was put up in a modification of Buck's extension with overhead traction, and within a few days the patient was able to assume a sitting position. A roentgenogram showed the typical changes of lateral bowing, excessive callus formation, honeycombed bone, thin cortices of the affected bones and a lateral displacement of the medullary cavity of the affected bones in

by administration of anterior pituitary extracts. Hennessy⁸ has found the endocrine organs to be normal at necropsy.

Some of the writers divide this disease into two or three types—congenital, late and idiopathic. There is a difference of opinion as to whether the conditions described under the terms of osteogenesis imperfecta congenita and osteogenesis imperfecta tarda, hereditary and non-hereditary osteopsathyrosis, fragilitas osseum, brittle bones and blue scleras represent the same disease and as to the propriety of labeling them simply as osteogenesis imperfecta. Rosenbaum⁷ quoted Glanzmann and Funk, who both stated that the two forms of this disease are separate entities and never occur in the same family. Rosenbaum then cited 5 cases which prove that the early and late types are both manifestations of the same disease. In the present study there was 1 patient (case 5) in whom the disease was of the so-called congenital type. This child was born with a kyphoscoliosis and fractures of both clavicles and lived only three days. In the other children the manifestations of the disease did not develop until later in life. Chont⁹ also reported a similar situation in the families he studied. According to Glanzmann and Funk, the congenital form is not hereditary, while the Lobstein type is hereditary. The congenital type is considered to be a recessive trait, and thus it is possible for either form of the disease to be manifested in any one family. Even when the trait is dominant, its manifestations may vary from generation to generation. This problem is still a moot one.

Bell pointed out that females are especially susceptible to the condition and constitute 55 per cent of all patients.¹⁰ The female is assumed to transmit the disease. The present study appears to confirm this observation. If all the manifestations are considered, 8 of the 11 females (73 per cent) were affected. Of the 8 females, all (100 per cent) had blue scleras, 5 (62 per cent) had multiple fractures, 3 (37 per cent) were deaf and 6 (72 per cent) had definite exophthalmos. Every child and grandchild of the patient in case 3 has a stigma of the disease. Only 1 child of the patient in case 4 has any of the stigmas.

It would be expected that 50 per cent of the offspring of a heterozygotic person with this condition mated with a normal person would have blue scleras and brittle bones. This was demonstrated to be true in many series of cases¹⁰ and is borne out in the present study. Hill and McLanahan¹⁰ concluded that each affected person has an affected parent and that the affected person, in turn, will have an equal number of affected and unaffected children. The unaffected children will not have affected descendants. A generation is never skipped.

8. Hennessy, J. P.: Osteogenesis Imperfecta, *Am. J. Obst. & Gynec.* **25**:590, 1933.

9. Chont, L. K.: Osteogenesis Imperfecta, *Am. J. Roentgenol.* **45**:850, 1941.

10. Hill and McLanahan,⁵ p. 44.

the fractured areas. After six weeks in this traction the patient was put in a spica cast and sent home.

He has since sustained a fracture of the left femur on Feb. 3, 1947, and one of the right femur on May 12. These were fractures number 11 and 12 respectively. Both followed minor trauma, and both occurred through the old fracture sites. They were treated, as before, with Buck's extension and overhead traction.

CASE 14.—A 3 year old girl entered the Toledo Hospital three days after her brother (the patient in case 13) had left, with her third fractured femur. When this child was 2 months old she also suffered a bilateral femoral fracture when she kicked the cradle. Since that time she had been active but had had no fractures. On the day of her admission to the hospital she slipped on a rug and fractured her left femur. Physical examination revealed no abnormalities except for blue scleras, blue tympanic membranes and decided exophthalmos. The findings in laboratory studies were normal. Roentgenograms made before the fracture revealed a definite tendency to fragile bones, but there was only slight bowing of the femurs and thinning of the cortices. A roentgenogram taken on admission showed a fracture of the midshaft of the left femur, with no displacement but with slight lateral bowing. The cortex in the region of the fracture was not unusually thin. The patient was given the same treatment as her brother, and at the time of the writing of this paper she was progressing well.

CASE 15.—The patient, a 3 month old boy, had had no fractures. He had blue scleras. Roentgenologic studies of the bones revealed none of the characteristic findings of osteogenesis imperfecta.

OTHER CASES.—The patients in cases 19, 20, 21 and 22 were children of the patient in case 18 by a second marriage. The patient in case 2 did not live with these children but was adopted by another family and thus lost track of her half brothers; she could remember no abnormalities in these people.

COMMENT

The cause of osteogenesis imperfecta is unknown, but it is assumed that there is some hereditary inferiority of the mesenchyme. Hill and McLanahan noted ⁵ that many other tissues of mesenchymal origin are not affected and that abnormalities have also been observed in tissues of endodermal and ectodermal origin. Farber and Margulis ⁶ expressed the opinion that the condition may be due either to some development defect or to a metabolic dysfunction or to both. They also stated that the poor mineralization of the bones may be due to an excessive excretion of calcium, a deficient absorption of calcium or an idiosyncrasy of alimentation. Other authors have suggested that there is a faulty metabolism which results from various endocrine upsets. Rosenbaum ⁷ stated that, while none of the endocrine organs can be incriminated per se, he has had some success in the treatment of patients with osteogenesis imperfecta

5. Hill, R. G., and McLanahan, S.: Brittle Bones and Blue Sclerae in Five Generations, *Arch. Int. Med.* **59**:41 (Jan.) 1937.

6. Farber, J. E., and Margulis, A. E.: Blue Sclerae, Brittle Bones and Deafness, *Arch. Int. Med.* **71**:658 (May) 1943.

7. Rosenbaum, S.: Osteogenesis Imperfecta and Osteopsathyrosis, *J. Pediat.* **25**:167, 1944.

Deformities are due to malunion rather than to softening of the bone, and hence reduction and care of the patient are important. Buck's extension with overhead traction seems to be more desirable than immobilization of the fractured extremity in a cast.

The deafness which is associated with this disease is caused by involvement of the otic capsule, which heals with sclerosis and produces a bony ankylosis of the stapediovestibular joint impairing the transmitting system of sound waves to the internal ear.⁹ It usually appears after the age of 20 and is progressive. No method of treatment has been successful.

The prognosis depends on several factors. If the patient can live a sheltered life, a minimum of fractures occur. If fractures do occur, proper care in reduction and immobilization may obviate deformities.

Persons who marry into families with osteogenesis imperfecta or persons who marry out of such families should be fully aware of the dangers to prospective children.

The treatment is largely empiric. Every form of medication has been tried, without outstanding results. Some authors report good results with the use of anterior pituitary extracts. Attempts to incriminate and remove various glands of internal secretion, such as the parathyroids and the thymus, have not been successful. Prophylaxis against injury and adequate reduction of the fragments when fractures occur represent the best form of treatment.

SUMMARY

Osteogenesis imperfecta occurring in a family of 17, representing five generations, has been studied. Roentgenographic studies were made on 9 of the 17, representing four generations. Of the 9 studied, 5 had evidences of recent or old fractures, and their bones showed typical changes of osteogenesis imperfecta. The remaining 4 revealed some of the other stigmas of the disease, but the bones were normal in appearance.

The members of this family showed the usual stigmas of osteogenesis imperfecta—blue scleras, brittle bones, deafness and hypertonicity of the ligaments. There was also a high incidence of exophthalmos.

The pathology of this disease has been adequately discussed elsewhere.¹¹ There is an apparent decrease in the number and efficiency of osteoblasts.

There are no typical laboratory findings in this condition. Puppel and others¹² report an increase in the blood iodine and also an increase in the urinary excretion of iodine. The calcium and phosphorus levels of the blood are variable. The level of serum phosphatase is slightly elevated, and there is usually a strongly positive Sulkowitch reaction.

The appearance of the bones in roentgenograms in osteogenesis imperfecta varies according to the number of fractures the patient has sustained. Chont⁹ discussed adequately the roentgenographic changes. The changes consist of generalized decalcification of the long bones, and deformation of the skulls of infants and adolescents, with an increase in the size of the cranial vault, prominent frontal and occipital bones and an increase in the number of wormian bones in some children. Early in the course of the disease there is a thinning of the cortex of the long bones. By the time the patient reaches the age of 5 or 6, the shafts have become thinner, but the width of the epiphysis remains normal, giving the bone a peculiar elongated appearance.

Following fractures, many of the bones are bent and there may be displaced fragments. The fractures are usually subperiosteal, with angulation of the fragments. With repeated fractures, there is a lateral displacement of the medullary canal at the site of the deformity. There are also narrow, transverse, triangular, decalcified, structureless areas extending a variable distance into the shaft from the convex side of the bent bone.

The bone trabeculation is scanty. Later in the course of the disease the cortex becomes thicker, with narrowing of the medullary canal and a "brittle" appearance of the affected bone.

In older children there may be the "honeycombed" bone type of Fairbanks. These bones are characterized by their extreme fragility and by the presence of cystic unossified areas. The honeycombed parts occur only after repeated fractures at the same site, and the areas of degeneration evidently follow bleeding into the bony structures.

Fractures occur in the proximity of the epiphysal-metaphysal junction. The metaphysis becomes thinner just before it reaches the epiphysal line and may account for fractures at this site.

After puberty, fractures occur less frequently. Comminuted and compound fractures are seldom observed, and nonunion is rare. Subperiosteal fractures with rotation of the fragments are common.

11. Key.⁴ Chont.⁹

12. Puppel, I. D.; Barron, L. E., and Curtis, G. M.: The Nature of Osteogenesis Imperfecta, *Am. J. M. Sc.* **190**:756, 1935.

The following presentation of cases is of interest in that the Guillain-Barré symptom complex developed in patients suffering from infectious mononucleosis. Neurologic complications led to death in both instances. An opportunity was presented to study the morbid anatomy encountered in infectious mononucleosis, a disease usually considered to be benign. The diagnosis was made on the basis of the postmortem findings and was substantiated in the first patient by a strongly positive reaction to the heterophile antibody test.

REPORT OF CASES

CASE 1.—A 22 year old white man was admitted to the Army Air Forces Station Hospital, Seymour Johnson Field, on Sept. 19, 1945, with the chief complaints of headache and fever. Eleven days prior to his admission he began to experience moderately severe frontal headaches. On several occasions he had chilly sensations associated with fever. There were also some pains described as aching in type in his elbow and knee joints. There was no history of previous serum therapy. His past history and family background were noncontributory.

Physical examination revealed a moderately ill white man in no great distress. The temperature, pulse rate and respiration rate were 102 F., 86 and 20, respectively. Aside from slight enlargement of the lymph nodes in the anterior cervical chain, the remainder of the physical examination revealed no abnormalities.

Laboratory findings on admission were as follows: Reaction to the Kahn test (qualitative) was doubtful. Urinalysis revealed no abnormalities. A complete blood count showed 4,400,000 red cells, with a hemoglobin content of 15.5 Gm. per hundred cubic centimeters, and 10,200 white blood cells, with 15 per cent polymorphonuclear cells, 1 per cent eosinophils, 2 per cent monocytes and 82 per cent lymphocytes. Many of the lymphocytes were atypical in form and conformed to the description of cells seen in infectious mononucleosis.

In view of the poorly defined clinical picture and because of the white blood cell count and the differential blood count, a tentative diagnosis of infectious mononucleosis was made. Thirty-six hours after the patient's admission to the hospital blood drawn for a heterophile antibody test was positive in a dilution of 1:1,792. (Unfortunately, since the specimen had to be sent to another laboratory the report was obtained several days after the patient died.)

The course in the hospital was as follows: On September 22 the patient complained of increasing headache. Examination revealed a moderate degree of nuchal rigidity, but that otherwise his condition remained unchanged. A lumbar puncture was productive of clear fluid under normal pressure, with a white blood cell count of 9,700, of which 94 per cent were lymphocytes and 6 per cent were polymorphonuclear leukocytes. The sugar content was normal and the protein increased. Smear and culture of the fluid proved to be sterile.

On September 23 a succession of neurologic symptoms and signs rapidly developed. He complained of tingling and numbness in his hands and feet, weakness in all four extremities and some difficulty in swallowing. His temperature, pulse and respirations were normal. The patient remained clear in sensorium although somewhat apprehensive. Examination revealed (1) complete paralysis of the right side of the face of a peripheral type; (2) moderate depression of the gag reflex; (3) hypesthesia in both hands and feet corresponding to the sensory components of the peripheral nerves, a symptom definitely against the diagnosis of poliomyelitis; (4) weakness of the muscles of the shoulder girdle, and (5) flaccid paralysis of the

NEUROLOGIC MANIFESTATIONS OF INFECTIOUS MONONUCLEOSIS

With Special Reference to the Guillain-Barré Syndrome

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INFECTIOUS mononucleosis has become a well known entity. The literature contains several articles describing in detail the classic clinical pictures. However, in cases which do not conform to the usual description the diagnosis is often confused or missed. In particular, this may be true when the symptoms are predominantly neurologic.

The involvement of the central nervous system may manifest itself by severe headaches, cranial nerve palsies, cerebellar signs and peripheral neuropathies. Thus there arises confusion with other diseases wherein neurologic symptoms are found. Infectious mononucleosis must be considered in the differential diagnosis of various types of lymphocytic meningitis, encephalitis, poliomyelitis, polyneuritis and the Guillain-Barré syndrome.

The Guillain-Barré syndrome was originally described as a peripheral radiculoneuritis, with findings of an increased protein level in the spinal fluid, associated with a normal or only slightly elevated white blood cell count. Symptoms of meningitis or meningoencephalitis with involvement of the cranial nerves are often present. There is considerable evidence at present that several agents or diseases can be responsible for the production of the symptom complex of infectious neuritis. For a more detailed discussion of the etiology of the Guillain-Barré syndrome and symptoms used in connection with it, the reader is referred to the review by Pullen and Sodeman.¹

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1. Pullen, R. L., and Sodeman, W. A.: Infectious Polyneuritis (Guillain-Barré Syndrome), *Am. J. M. Sc.* **211**:110 (Jan.) 1946.

and past history were noncontributory. Except for moderate fever and redness of the throat, the physical examination revealed nothing abnormal. With nonspecific therapy, he recovered sufficiently to be discharged from the hospital on December 1. Culture of material from the throat at this time did not reveal *Corynebacterium diphtheriae*.

On December 16 the patient was readmitted to the same hospital because of an increasingly severe sore throat. He also complained of soreness and weakness of the muscles of the lower extremities. Physical examination at this time revealed the following picture: The throat was moderately reddened. The cervical lymph nodes were enlarged. In the chest the lungs were clear, but over the cardiac apex a loud, blowing systolic murmur was heard. The blood pressure was normal. Examination of the abdomen revealed no abnormalities. The muscles of the calves and thighs were tender to pressure. The muscles of all four extremities exhibited weakness. The deep reflexes were absent. No sensory changes could be demonstrated.

Laboratory examinations gave the following results: In the spinal fluid the sugar content was 50 mg., the total protein content 74 mg. and the chloride content 627 mg. per hundred cubic centimeters. The white blood cell count was 8,000 (no differential count was done). A culture and smear of material from the throat failed to reveal *C. diphtheriae*. The electrocardiogram was normal.

The patient was given 40,000 units of diphtheria antitoxin and adequate doses of penicillin. During the next twenty-four hours he became progressively weaker. Transfer to another hospital was effected on December 19.

Physical examination on his arrival at the hospital revealed an acutely ill white man. The palate and pharynx at this time were diffusely reddened, edematous and covered with patches of white exudate. The cervical nodes were enlarged. In the thoracic wall there was absence of intercostal action of the upper two thirds and weakness in the lower third. Movements of the diaphragm were accomplished without apparent restriction. The lungs, heart and abdominal organs seemed normal. Aside from the intercostal difficulty, the involvement of the nervous system consisted in weakness of the muscles of the upper extremities, definite paralysis of the muscles of the lower extremities of the flaccid type and absence of the deep reflexes. Despite complaints of transient paresthesias of the hands and feet, objective sensory changes could not be demonstrated.

On December 19 the following laboratory data were obtained: Smear and culture were negative for *C. diphtheriae*. A complete blood count showed 4,740,000 red blood cells, with a hemoglobin content of 90 per cent, and 9,900 white blood cells, with 56 per cent neutrophils, 39 per cent lymphocytes and 5 per cent monocytes. The urine was normal, and a blood culture showed no growth.

In the next twenty-four hours the patient went rapidly downhill, and he died in respiratory failure on December 20. The clinical diagnosis was infectious polyneuritis of Guillain-Barré.

Pathologic Diagnosis.—Briefly, the pathologic diagnosis was as follows: Conditions in the respiratory system were acute nasopharyngitis, acute laryngitis, acute tracheobronchitis and atelectasis of the lower lobes of both lungs and the middle lobe of the right lung; in the spleen and hemopoietic tissues, acute splenitis, acute passive congestion of the spleen and acute lymphadenitis of the cervical, tracheobronchial, bronchopulmonary and abdominal lymph nodes; in the liver, acute passive congestion and in the nervous system, infectious polyneuritis (Guillain-Barré syndrome).

The neuropathologic diagnosis was based on the finding of: (1) congestion of the leptomeninges; (2) increased congestion, petechial hemorrhages and occasional

muscle groups of all four extremities, with absence of the triceps, biceps, patellar and ankle reflexes. Respiratory movements were accomplished without difficulty. There was no involvement of the thoracic and abdominal musculature or of the rectal and urinary sphincters. Fibrillary tremors were not demonstrable. The picture was one of an extensive, rapidly progressing peripheral neuropathy associated with meningoencephalitis.

Because of the alarming progression of signs, the patient was transferred to a hospital equipped with a mechanical respirator. Despite the absence of the typical albuminocytologic dissociation in the spinal fluid, the diagnosis on transfer was "infectious neuritis of the Guillain-Barré type."

On September 24 the patient showed progressive deterioration, with complete quadriplegia, dysphagia and paralysis of the diaphragm. He was placed in the respirator, and other supportive measures were instituted. The laboratory findings at this time were as follows: A blood count showed 4,600,000 red blood cells, with a hemoglobin content of 15 Gm. per hundred cubic centimeters, and 13,300 white blood cells, with 21 per cent polymorphonuclear cells and 79 per cent lymphocytes. The spinal fluid contained 36,000 white blood cells, with 2 per cent polymorphonuclear cells and 98 per cent lymphocytes, and a total protein content of 81 mg. per hundred cubic centimeters. Culture of the fluid was sterile, and a culture of the blood also showed no growth.

On September 25, despite treatment, the patient died in respiratory failure.

Autopsy.—Three hours after death autopsy was performed. The positive findings were listed as follows:²

Lungs: The lungs showed early patchy bronchopneumonia, most pronounced in the lower lobes.

Cardiovascular System: Aortic atheroma was evidenced in the cardiovascular system, which was otherwise normal.

Spleen: Vascular changes and enlargement such as is described in association with infectious mononucleosis (see explanation) were seen in the spleen.

Liver: Examination of the liver revealed interstitial hepatitis associated with vascular changes comparable with those seen in the spleen.

Bone Marrow: There were reactive changes in the bone marrow compatible with a diagnosis of infectious mononucleosis.

Brain: In the brain there was increased vascular reaction of the pia-arachnoid. There were petechial and small perivascular hemorrhages throughout the cerebral cortex. In the cerebellum there occurred moderate degeneration of the cells of Purkinje. In the spinal cord degeneration and atrophy of the anterior horn cells were occasionally noted. Microscopic examination of certain peripheral nerves revealed interstitial fibrosis and cellular infiltrations.

The remainder of the organs were normal. The changes in the nervous system were comparable to those seen in the Guillain-Barré syndrome.

Changes described in the spleen and liver were considered pathognomonic for infectious mononucleosis, according to criteria set down by Smith and Custer.³

*CASE 2.*⁴—A 21 year old white man was admitted to a station hospital on Nov. 28, 1945, complaining of chilly sensations, headache and weakness. His family

2. Both in the first and second cases the pathologic reports are limited to summaries. Full descriptions of the gross and microscopic changes will appear in another paper concerning the pathologic aspects of infectious mononucleosis.

3. Smith, E. B., and Custer, R. P.: Rupture of the Spleen in Infectious Mononucleosis: A Clinicopathologic Report of Seven Cases, *Blood* 1:317 (July) 1946.

4. This case was abstracted from the files of the Army Institute of Pathology, Colonel J. E. Ash, Medical Corps, Director.

there occurs moderate cellular infiltration of the capsule and considerable hyperplasia of the red pulp. Typical vascular changes are seen in the adventitia of the trabecular arteries, in which infiltrations of mononuclear cells are encountered. The subintima of the trabecular veins present a similar situation. Vessels in the portal areas of the liver show changes like those in the spleen. These findings were present in the 2 cases reported here.

The infective agent may attack any organ or system. Involvement of the nervous system is not uncommon in infectious mononucleosis. The most frequent manifestation is lymphocytic meningitis. Reports of manifestation with this case have been made by Epstein and Dameshek,⁷ Gsell,⁸ Huber,⁹ Thelander and Shaw¹⁰ and Coogan and his associates.¹¹ The meningitis may occur at any time during the course of the disease. The symptoms of meningeal involvement may be absent, and the complication may be found on routine lumbar puncture. In others the usual picture of meningismus is present during the course of the disease. The spinal fluid is not characteristic except for the predominance of lymphocytes in the smear. The protein content may be normal or elevated; the sugar and chloride levels are normal, and the cultures are sterile.

The involvement of the nervous system may be so extensive as to produce symptoms of encephalopathy in addition to those of meningitis. A case with cerebellar symptoms was reported by Landes and others.¹² Patients presenting unilateral ptosis,⁷ palsy of the peripheral facial nerves⁸ and weakness of the pharyngeal muscles (case 1) have either direct nuclear involvement or disease of the nerve distal to the nucleus. Aside from the focal signs, patients may exhibit more general indications of cerebral disease, such as diplopia, delirium, lethargy and impaired memory.

A third type of neurologic disorder found on occasion is peripheral neuropathy. The cases reported previously illustrate widespread polyneuritis. Disease of the peripheral nerves in infectious mononucleosis

7. Epstein, S. H., and Dameshek, W.: Involvement of the Central Nervous System in a Case of Glandular Fever, *New England J. Med.* **205**:1238 (Dec. 24) 1931.

8. Gsell, O.: Serous Meningitis in Pfeiffer's Glandular Fever (Infectious Mononucleosis), *Deutsche med. Wchnschr.* **63**:1759 (Nov. 19) 1937.

9. Huber, W.: Contribution to the Problem of Serous Meningitis in Pfeiffer's Glandular Fever, *Schweiz. med. Wchnschr.* **68**:892 (July 23) 1938.

10. Thelander, H. E., and Shaw, E. B.: Infectious Mononucleosis with Special Reference to Cerebral Complications, *Am. J. Dis. Child.* **61**:1131 (June) 1941.

11. Coogan, T. J.; Martinson, D. L., and Matthews, W. H.: Neurological Symptoms of Infectious Mononucleosis, *Illinois M. J.* **87**:296 (June) 1945.

12. Landes, R.; Reich, J. P., and Perlow, S.: Central Nervous System Manifestations of Infectious Mononucleosis: Report of a Case, *J. A. M. A.* **116**:2482 (May 31) 1941.

degeneration of the ganglion cells throughout the cerebrum, pons and medulla; (3) inflammation of the leptomeninges, small hemorrhages and occasional degeneration of the ganglion cells in the posterior horns at several levels of the spinal cord, and (4) perivascular cellular infiltrations of the sheaths and swelling of the myelin sheaths of several peripheral nerves.

In summary of the second case, the diagnosis of Guillain-Barré syndrome was made from the clinical picture. This diagnosis was substantiated by the autopsy. The diagnosis of infectious mononucleosis was made by the pathologist after detailed examination of the spleen and lymph nodes. Unfortunately, a heterophile antibody test was not done to substantiate the diagnosis.

Virus studies were accomplished by the injection of material from the brain and spinal cord into mice and guinea pigs. No virus could be isolated.

COMMENT

The etiology of infectious mononucleosis remains unknown. The disease may occur sporadically or appear in small epidemics. Characteristically, it affects children and young adults. The manifestations are varied, but in general they fall into three main categories. There are: (1) the glandular or Pfeiffer type, with either slowly or rapidly developing generalized lymphadenitis and splenomegaly; (2) the anginose or pharyngeal variety, resembling those of acute ulcerative tonsillitis, and (3) the febrile type, often treated as indicative of fever of undetermined origin. Many other cases cannot be classified so simply. In reviewing the subject, Bernstein⁵ has pointed out the common occurrence of such symptom complexes as hepatitis with or without icterus, cutaneous eruptions of various kinds, hemorrhagic phenomena and neurologic concomitants. The prognosis is almost always favorable for complete recovery. The diagnosis may be suggested by the white blood cell count and blood smears exhibiting either a relative or absolute predominance of mononuclear cells with atypical lymphocytes. In most cases the diagnosis can be substantiated by the finding of a positive heterophile antibody reaction of high titer. The treatment is purely symptomatic.

Known facts about the pathologic process in infectious mononucleosis are meager because of the rarity of death from this disease. Most of the information, based on biopsies of lymph nodes and punctures of the bone marrow, revealed infiltration of mononuclear cells.⁵ In a case in which death was due to rupture of the spleen Ziegler⁶ noted infiltration of mononuclear cells in many organs and tissues, presenting a picture of a generalized infection with specific localizations. Lesions of the spleen and liver as described by Smith and Custer³ are considered characteristic of infectious mononucleosis. In the spleen

5. Bernstein, A.: Infectious Mononucleosis, *Medicine* **19**:85 (Feb.) 1940.

6. Ziegler, E. E.: Infectious Mononucleosis: Report of a Fatal Case with Autopsy, *Arch. Path.* **37**:196 (March) 1944.

limited to the nervous system. Infectious mononucleosis must be considered as a possible factor in the differential diagnosis of infectious neuronitis. In addition, when symptoms or signs of peripheral neuritis do arise in the course of infectious mononucleosis, one must be aware of the danger of paralysis of the respiratory system and death.

SUMMARY

1. Neurologic symptoms and symptom complexes in infectious mononucleosis have been briefly discussed.

2. In evidence that the Guillain-Barré syndrome may occur during the course of infectious mononucleosis, 2 cases are presented. Respiratory failure was responsible for the fatal outcomes in both cases. The essential pathologic findings are recorded.

3. The Guillain-Barré syndrome is the neurologic manifestation of many diseases of different origin.

4. Infectious mononucleosis must be considered in the differential diagnosis of infectious neuronitis.

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has been reported by Zohman and Silverman¹³ and by Coogan and others.¹¹ Recovery was the rule, in contrast to the residuals usually found in the wake of acute anterior poliomyelitis in which the disease attacks the spinal cord.

Infectious mononucleosis with neurologic complications presents problems in differential diagnosis. When lymphocytic meningitis is present, abortive poliomyelitis, tuberculous meningitis, benign lymphocytic choriomeningitis, "serous" meningitis and the meningitis that may accompany the infectious exanthems must be ruled out. However, with peripheral polyneuritis the problem is more difficult. More common causes of meningoencephalitic neuropathies to be considered are acute paralytic poliomyelitis, polyneuritis of toxic, metabolic or infectious origin and the Guillain-Barré syndrome.

In the cases presented it is of interest to note the striking resemblance of the neurologic signs to those in patients with the Guillain-Barré syndrome as described by McDonald and Taylor¹⁴ and Lewey.¹⁵ From the review of Lewey's article the impression is gained that the Guillain-Barré symptom complex is actually a multitude of diseases having a common denominator in the albuminocytologic dissociation of the spinal fluid. This fact is borne out by the recent report of cases of polyneuritis occurring as a sequela of diphtheria¹⁶ and as a neurologic complication of infectious mononucleosis (case by Landes and others and present cases).

From the standpoint of pathologic change, the nervous system in infectious polyneuritis usually exhibits congestion of the meninges, cerebrum and spinal cord. However, more pronounced are the changes in the peripheral nerves, in which edema of the nerve bundles, congestion, focal cellular infiltrations and swelling and beading of the myelin sheaths may be seen.¹ In addition it must be remembered that the toxic or infectious agent producing the nervous changes may also attack the viscera. Sabin and Aring¹⁷ recorded such involvement in patients dying from the Guillain-Barré syndrome.

The evidence presented indicates the necessity for viewing the Guillain-Barré syndrome as a generalized disease rather than as one

13. Zohman, B. L., and Silverman, E. G.: Infectious Mononucleosis and Encephalomyelitis, *Ann. Int. Med.* **16**:1233 (June) 1942.

14. Taylor, E. W., and McDonald, C. A.: The Syndrome of Polyneuritis with Facial Diplegia, *Arch. Neurol. & Psychiat.* **27**:79 (Jan.) 1932.

15. Lewey, F. H.: What Is the Guillain-Barré Syndrome? *J. Pediat.* **26**:165 (Feb.) 1945.

16. Delp, M. H.; Sutherland, G. P., and Hashinger, E. H.: Post-Diphtheritic Polyneuritis: A Report of Five Cases with Albumino-Cytologic Dissociation Simulating the Guillain-Barré Syndrome, *Ann. Int. Med.* **24**:618 (April) 1946.

17. Sabin, A. B., and Aring, C. D.: Visceral Lesions in Infectious Polyneuritis, *Am. J. Path.* **17**:469 (July) 1941.

EPIDEMIOLOGY

Table 1 summarizes the main epidemiologic findings. The average age of the patients of the whole four year period was 24.79 years. The range of the ages was from 18 to 54 years. The average age for each year, however, shows a steady decline from 27.83 years in 1942 to 22.27 in 1945. It is interesting to note the relationship of the 1943 and 1944 age averages and the accompanying proportion of white and Negro patients. There is almost a complete reversal of the ratio of white to Negro patients in the two years, but the ages remained the same. From the race ratio it is seen also that with the exception of 1943 there was a steady increase in the proportion of Negroes admitted from 1942 through 1945. All of the factors influencing this trend are

TABLE 1.—*Epidemiologic Data*

Years	1942	1943	1944	1945	Total Number or Average
Total number of patients.....	254	415	995	836†	2,500
Number of cases tabulated.....	254	185	306	100*	845
Average age.....	27.83	24.52	24.53	22.27*	24.79
Race ratio (white/Negro).....	63/37	90/10	18.5/81.5	8/92*	45/55
Average months of service.....	13.06	10.83	8.84	5.22*	9.49
Number outside "South".....	21.56%	54.62%	13.68%	29.95%
Epididymo-orchitis	21.26%	24.33%	27.03%	24.28†	25.12
Clinical meningitis.....	14(5.5%)	8(1.9%)	22(2.2%)	(33%)*	44(2.6%)†
Average total days in the hospital....	14.38	18.75
Days in the hospital (uncomplicated)...	13.34	13.80
Days in the hospital (complicated).....	16.48	19.85	24.30

† Data obtained from the registrar's records.

* Holden, Eagles and Stevens' series.

† Cases in 1945 not included (total, 1,664).

not known, and since the distribution of the general population of the post during this interval is not known, no definite conclusions can be drawn.

McGuinness and Gall,² from their study in Camp McCoy, Wis., stated that mumps in epidemic form is unlikely to occur except among soldiers from rural areas of the South and Southwest. In an effort to confirm this, the patients from the "South" were separated and the number from elsewhere were tabulated in descending order according to the year and to their native states. The following states were arbitrarily considered as the "South": Virginia, North Carolina, South Carolina, Georgia, Florida, Tennessee, Mississippi, Alabama and Louisiana. In table 1 can be seen the distribution of cases outside of the South, which was as follows: 21.56 per cent in 1942, 54.62 per cent

2. McGuinness, A. C., and Gall, E. A.: Mumps at Army Camps in 1943, War Med. 5:95 (Feb.) 1944.

ANALYSIS OF A FOUR YEAR EPIDEMIC OF MUMPS

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AT FORT BENNING, GA., in the winter of 1941 there appeared an unusual increase in the number of cases of mumps, which reached a peak for that season of 49 new cases in the month of April 1942. There followed a cyclic rise and fall in the number of cases in the next three years, but the incidence never returned to the corresponding seasonal level at which it had been prior to 1941. The apex of the epidemic was reached in March 1944, when the maximum of 289 new patients were admitted during the month. Over the whole four year period a total of 2,500 patients were admitted. The seasonal distribution of the cases from 1942 through 1944 is shown in figure 1. A considerable proportion of these patients were admitted from the Reception Center, and during the last two years practically 90 per cent of the patients were from this center or its associated training schools. With these facts in mind, this might be considered as an "endemic epidemic," with the endemic focus being the Reception Center. Because of the duration of this epidemic, or series of epidemics as some may prefer to call it, it was thought desirable to analyze the data from these 2,500 cases in a search for any new clinical or epidemiologic facts that might be present.

The 2,500 cases were distributed through the four years as follows: 254 in 1942; 415 in 1943; 995 in 1944, and 836 in 1945. The data on each consecutive case in 1942 were recorded on a large analytic chart. The data from the first 100 consecutive cases of 1943 were likewise recorded. Thereafter charting was done only for cases with some unusual manifestation, although each clinical record was reviewed thoroughly. The majority of the statistical deductions are based on these three groups, with a total of 1,664 cases. For administrative reasons the charts of the 1945 group were not available, and the data used to represent these 836 cases were secured from the registrar's official statistics and from analytic data obtained from a report by Holden, Eagles and Stevens¹ of 100 consecutive admissions during the height of the 1945 peak of this epidemic.

1. Holden, E. M.; Eagles, A. Y., and Stevens, J. E., Jr.: Mumps Involvement of the Central Nervous System, *J. A. M. A.* **131**:382 (June 1) 1946.

decreased throughout the four year period. In 1942 the average duration of service at the time of admission was 13.06 months, and by 1945 it had fallen to only 5.22 months.

The seasonal distribution fell into the usually expected pattern and can be seen for the years 1942 to 1944 in figure 1.

CLINICAL COURSE

The general course of the disease can be described as being typical of that usually seen in cases of mumps in adults. The patients were admitted from outlying dispensaries by way of "sick call" to the hospital, where they were isolated. The average number of days of illness before hospitalization was only 1.53; however, it varied from none to 14 days. Patients waiting 10 to 14 days after the onset of salivary involvement before seeking hospitalization were usually found to have orchitis and little if any salivary enlargement. They usually gave one of the following histories: (1) they had had little salivary swelling and didn't know what it was; (2) they had applied to "sick call" and the doctor failed to make the diagnosis, or (3) they had requested permission of the sergeant to report to "sick call" and had been refused. Usually, however, the presenting complaints were of swollen and painful jaws, headache and a low to moderate degree of fever.

No reliable data were obtained in relation to the duration of rest in bed, but general observation seemed to confirm previous experiments showing no relationship with the incidence of orchitis. Rest in bed with bathroom privileges was the general rule for any febrile episode and until the greater part of the salivary swelling had disappeared. After that it was practically impossible to impose rest in bed on the majority of the patients.

The incidence and distribution of the salivary glands involved are shown in table 2. The figures correspond fairly closely with those of McGuinness and Gall² and Haerem.³ Following the example of the first two authors, the total days and "units" of fever were tabulated for each of the various manifestations of the disease. The unit is considered as 1 degree (F.) of temperature above normal for each day. By this method one gets another indication of the severity and toxicity of the disease. For example, it reveals the difference between one patient who had a temperature of 100 F. for three days and another who had fever for the same number of days, but with a temperature of up to 103 F. each day. The units would be 2 per day, a total of 6, for the first patient, while for the second patient there would be 5 units per day, or a total of 15. When two manifestations occurred

3. Haerem, A. T.: Observations on Mumps in Soldiers, *Mil. Surgeon* **97**:33 (July) 1945.

in 1943 and 13.68 per cent in 1944. Thus the percentage as seen in 1943 would not uphold the aforementioned statement. Even with the inclusion of those from Texas, Oklahoma, Arkansas and Missouri as representing the Southwest, the percentage is still 35.6 per cent of all patients from elsewhere than the South and Southwest.

The duration of hospitalization for all patients seen in 1942 averaged 14.38 days. When differentiation is made between the simple forms of the disease and those with unusual manifestations, the duration in the "uncomplicated" cases averaged 13.34 days and in the compli-

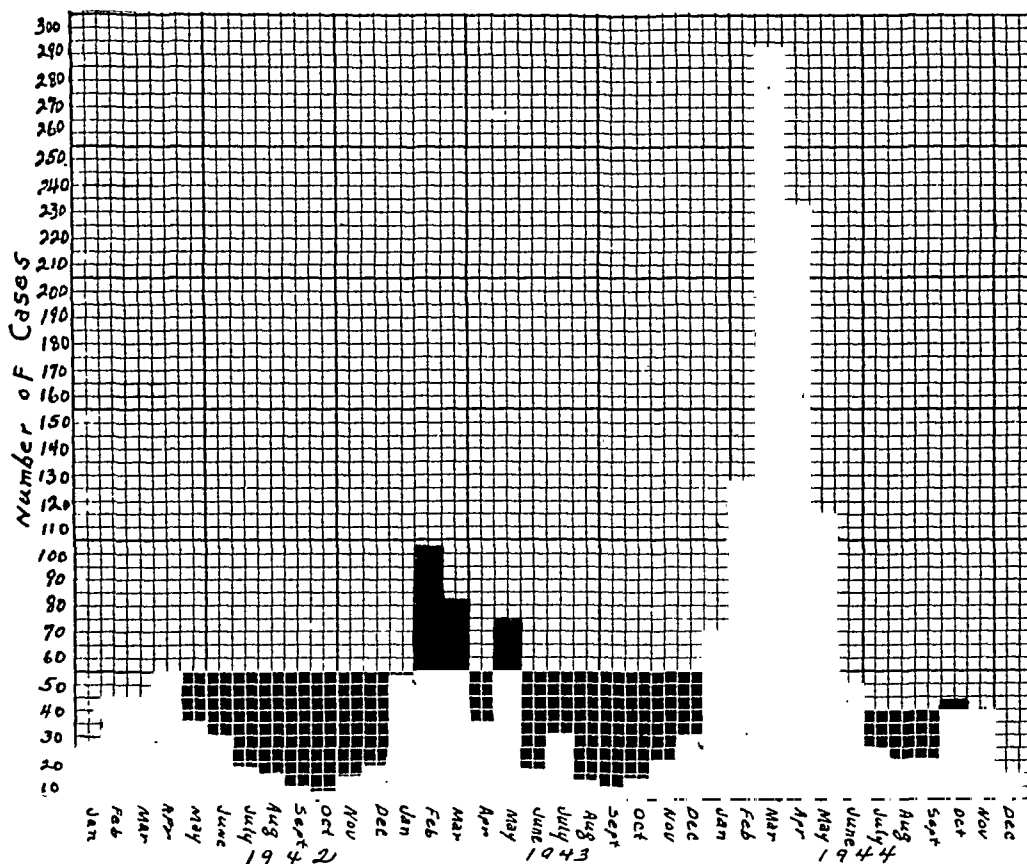


Fig. 1.—Seasonal distribution in epidemic of mumps over three years.

cated ones 16.48 days. Among the first 100 cases in 1943 the average for the uncomplicated attacks was found to be 13.80 days—probably no significant variation from that of 1942. However, in the complicated cases in 1943 and 1944 the disease was of progressively increasing duration, the average being 19.85 days in 1943 and 24.30 in 1945. Although there were several extraneous factors which might have affected these figures, the possibility of an increasing virulence of the infection is definitely suggested.

Similar to the occurrence in the age incidence, the duration of service at the time of the patient's admission to the hospital steadily

variation in the occurrence of orchitis, a thorough check was made of the first 400 patients in this series admitted to the hospital. No significant grouping of the cases of orchitis was found. The distribution of the cases can be seen from table 4 and confirms previous reports as to the various incidences. However, the yearly averages show an increasing incidence of epididymo-orchitis from 21.26 per cent in 1942 to 27.03 per cent in 1944, again suggesting an increasing virulence of the virus as the epidemic progressed. The day of onset of orchitis in relation to that of parotitis remained fairly constant, with an average of 4.5 days after salivary swelling began. The extremes are remarkable, however, ranging from 14 days before salivary involvement to 25 days after. Patients in whom the complication developed after three weeks

TABLE 4.—*Distribution of Cases of Epididymo-Orchitis*

Year.....	1942		1943		1944		1945	Total	
Total number of cases.....	254		415		995		836	2,500	
Number of cases of orchitis (per cent).	54 (21.26%)		102 (24.33%)		269 (27.03%)		203 (24.28%)	628 (25.12%)*	
	Num- ber	Per Cent	Num- ber	Per Cent	Num- ber	Per Cent		Num- ber	Per Cent
Distribution of orchitis.									
Right side.....	24	44.4	55	53.9	120	44.9	...	199	46.8
Left side.....	25	26.3	32	31.4	103	33.2	...	165	38.8
Bilateral.....	5	9.3	15	14.7	43	15.9	...	63	14.8
Undesignated.....	0	0	3	1.1
Time of onset after parotitis									
Average.....	3.55 days		5.3 days		4.6 days			4.5 days	
Range.....	14 days before to 11 after		0 to 20 days after		0 to 25 days after			14 days before to 25 days after	
Fever	Days	Units	Days	Units	Days	Units		Days	Units
Average.....	3.81	12.9	3.36	11.6	3.8	13.3	...	3.66	12.6
Range.....	0 to 7	0 to 34	1 to 9	1 to 38	0 to 9	0 to 42	...	0 to 9	0 to 42
Miscellaneous.....	5 cases of orchitis without parotitis Only 2 cases of total number operated on								

* Four hundred and twenty-five instances of orchitis occurred in the first three years in a total of 1,664 patients.

were, as pointed out by McGuinness,² practically afebrile, but no essential differences were noted in those with an earlier onset. The average duration of fever due to the manifestations of orchitis was 3.66 days, with a range of 0 to 9 days, and the average degree was 12.59 units, with a range of 0 to 42. Out of 995 cases in 1944 there were 5 instances of orchitis without involvement of the salivary glands and in 1 of these the patient had an associated meningoencephalitis. One similar case,⁴ not included in this series, was reported because of meningeal signs present on the patient's admission to the hospital and the subsequent development of epididymo-orchitis. The cause in this case was definitely established by a positive reaction to complement fixation tests for mumps.

4. Eagles, A. Y.: An Unusual Case of Mumps Without Parotitis, Bull. U. S. Army M. Dept. 5:598 (May) 1946.

simultaneously, the fever was tabulated to the credit of the more severe syndrome. In table 3 is seen the distribution of fever in the involvement of the salivary glands over the three year period. The average number of days of fever in these so-called uncomplicated cases is 2.11, and the average number of units is 4.99. However, it should be noted that, while the average number of days of fever varied little from year to year, there was a definite increase in the average number of units of fever in these "uncomplicated cases"—from 3.55 in 1942 to 7.14 in 1944. The range of days extends from 0 to 9, while that of the units

TABLE 2.—*Involvement of the Salivary Glands*

Year (Number of Tabulated Cases in Parentheses)	1942 (254)		1943 (185)		1944 (306)		1945 (100)		Total (845)	
	Num-ber	Per Cent	Num-ber	Per Cent	Num-ber	Per Cent	Num-ber	Per Cent	Num-ber	Per Cent
Parotid, bilateral.....	134	52.75	125	67.57	203	66.3	68	68	530	62.7
Right parotid.....	46	18.11	27	14.59	52	16.9	16	16	141	16.7
Left parotid.....	71	27.95	30	16.22	41	13.4	16	16	158	18.7
Submaxillary, bilateral.....	6	2.36	15	8.05	17	5.6	38	5.1
Right submaxillary.....	11	4.33	4	2.16	13	4.2	28	3.6
Left submaxillary.....	12	4.72	10	5.42	13	4.2	35	4.7
Parotid and submaxillary.....	22	8.66	23	12.43	39	12.7	84	11.3
Submaxillary only.....	3	1.18	3	1.62	4	1.4	10	1.3
Without involvement of the salivary glands.....	0	0	0	0	6*	2.0

* Of these, 4 had epididymo-orchitis and 2 had meningoencephalitis.

TABLE 3.—*Duration and Degree of Fever in Involvement of the Salivary Glands*

Year.....	1942		1943		1944		Total	
Number on which data were obtained	231		156		245		632	
"Uncomplicated" Fever	Average	Range	Average	Range	Average	Range	Average	Range
Days.....	1.9	0 to 8	2.25	0 to 9	2.20	0 to 7	2.11	0 to 9
Units.....	3.55	0 to 23	4.28	0 to 11	7.14	0 to 18	4.99	0 to 23
Total Fever								
Days.....	3.1	0 to 11
Units.....	7.02	0 to 36

extends from 0 to 23. The complete data in relation to fever are unavailable except for the year 1942, when the total number of days of fever was 3.1 and the number of units 7.02, with a corresponding total range of 0 to 11 days and 0 to 36 units.

EPIDIDYMO-ORCHITIS

There were 425 instances of epididymo-orchitis in the 1,664 cases of the first three years, which were individually reviewed; there were 203 more instances of epididymo-orchitis in the 1945 series of 836 cases, which could not be reviewed. This gives a total of 628 cases of orchitis out of the series of 2,500, making an incidence of 25.12 per cent. Because a general impression had been obtained of an irregular cyclic

presternal edema occurred in 30, or 6 per cent of their whole group. This syndrome is a symmetric painless pitting edema of the soft tissues overlying the sternum, associated with swelling of salivary glands due to mumps. In by far the greatest number of cases the condition is associated with submaxillary glandular involvement. The edema persists for five days on the average. The onset usually occurs five to six days after the appearance of the glandular swelling. The distribution and pitting nature of the edema may be seen from the accompanying photographs of a patient in whom the condition was of average severity.

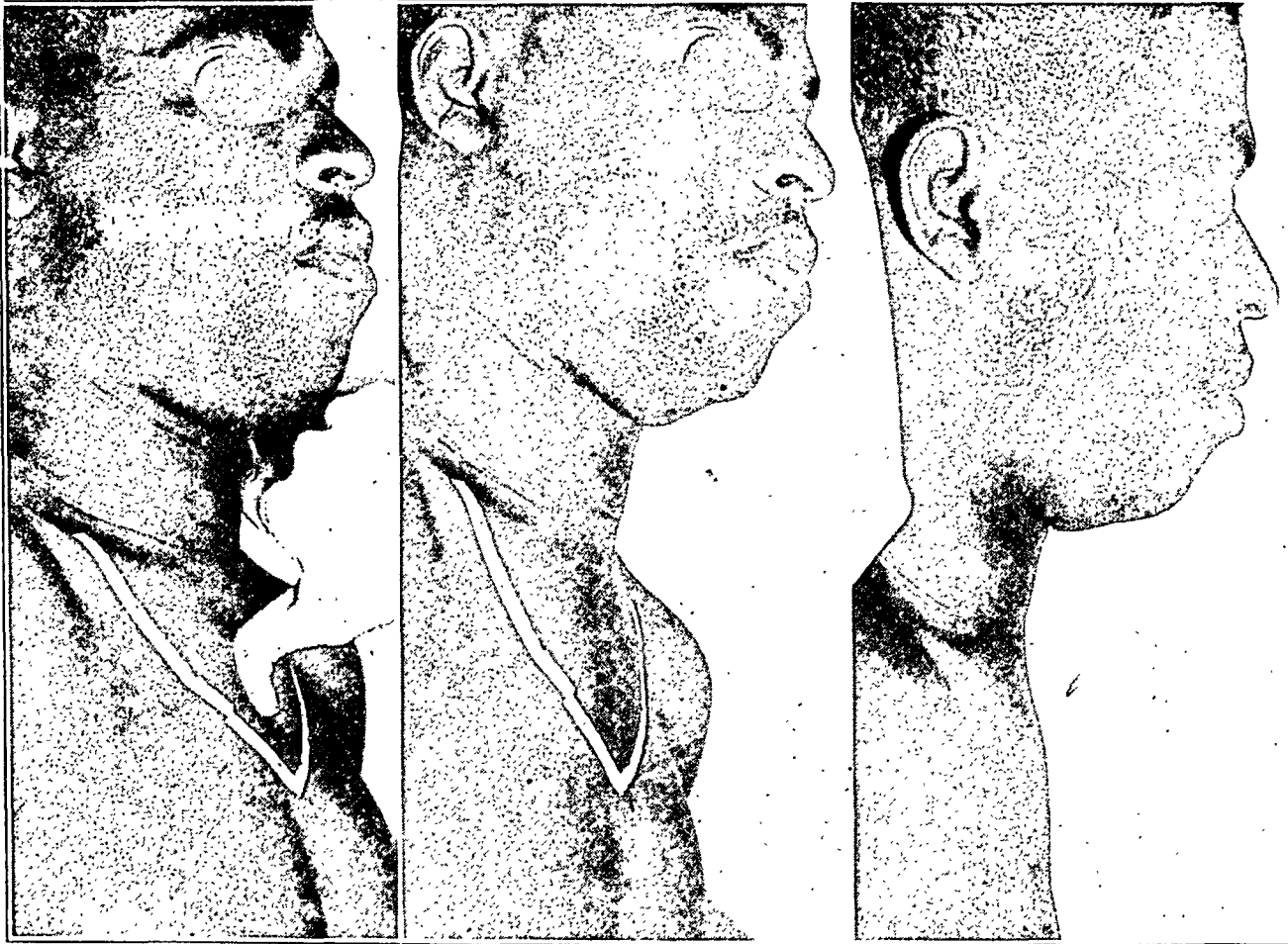


Fig. 2.—Patient with presternal edema of average severity. Note distribution and pitting. (Photo by U. S. Army Signal Corps.)

Although dangerous symptoms are not usually seen with this syndrome, on rare occasions a serious danger of tracheal obstruction from the increased pressure within the tissues of the neck may be observed. The cause is thought to be obstruction to lymphatic drainage by the salivary glands concerned.

In the review of the 1,664 cases occurring during the entire period 1942 through 1944, only 21 instances of presternal edema were found

Out of the series of 425 cases of orchitis reviewed, in 63 the condition was bilateral. From the entire series of 628 patients, only 2 underwent the surgical treatment of incision of the tunica albuginea, as advised by Wesselhoeft and Vose.⁵ Both of these had bilateral orchitis, but the operation was bilateral in only 1. Pain subsided promptly in each case, although fever persisted for twenty-four hours following operation. In the patient with a unilateral operation the incision healed in six weeks, while in the patient with the bilateral operation it healed in four weeks. Follow-up was available on only 1—a white enlisted man of the medical department, stationed at the hospital. One and a half years later, when questioned, he reported a softness present in the testicle operated on, with mild residual soreness. He also claimed some diminution of libido, although he admitted it might be psychogenic in origin. On several occasions surgical treatment was advised for patients with extremely swollen testicles, after a thorough explanation of the reason, methods and results to be expected therefrom. Most of them refused the treatment. Symptomatic therapy of orchitis consisted of strict rest in bed with an adhesive bridge for support, application of an ice bag locally and liberal use of acetylsalicylic acid and small doses of codeine as necessary. In extreme instances of high fever, nausea and vomiting, administration of parenteral fluids became necessary, as it was not uncommon to observe temperatures of 105 F. or more with this episode.

From the report of Gellis and others⁶ on two groups of patients in the 1944 series of this epidemic, it is seen that the use of gamma globulin, when available, is worth while in the prevention of orchitis. In 51 patients treated with 20 cc. of gamma globulin made from mumps convalescent serum, orchitis occurred in 7.8 per cent, while in the controls it occurred in 27.4 per cent. In 67 patients treated with 50 cc. of gamma globulin from pooled normal human plasma the percentage in which orchitis occurred was 20.9, compared with 26.8 per cent for the controls. The first group received the equivalent of 400 cc. of convalescent serum globulin or the equivalent (in antibody content) of 4,000 cc. of normal pooled plasma. Despite these encouraging results, the practical application awaits the development of an adequate supply of the fractionated protein.

PRESTERNAL EDEMA

Gellis and Peters⁷ in the early part of 1944 carefully examined 500 patients in this same epidemic and from their personal records found that

5. Wesselhoeft, C., and Vose, S.: Surgical Treatment of Severe Orchitis in Mumps, *New England J. Med.* **227**:277 (Aug. 3) 1942.

6. Gellis, S. S.; McGuinness, A. C., and Peters, M.: A Study of Prevention of Mumps Orchitis by Gamma Globulin, *Am. J. M. Sc.* **210**:661 (Nov.) 1945.

7. Gellis, S. S., and Peters, M.: Mumps with Presternal Edema, *Bull. Johns Hopkins Hosp.* **75**:241 (Oct.) 1944.

From the previously reported results in 100 cases studied from the 1945 series,¹ no correlation was expected in this series between the white blood cell count and any of the manifestations of mumps. The average white blood cell count in all cases in 1942 was 6,780, while in 1944 in the "complicated" cases only it was 6,442. The average differential count in all cases in 1942 was 55.6 polymorphonuclear cells and 38.6 lymphocytes, and in the 1944 complicated cases alone the ratio was 55.8 to 39.6.

No adequate study was made of the relationship of serum amylase content to the various manifestations of the disease. A general impression was obtained of the highest values for serum amylase being associated with the height of salivary swelling, similar to that found by Haerem.³ In Bang and Bang's⁹ series of cases of mumps, 60 per cent (230 of 371) of the patients with salivary involvement had an elevated urinary diastase content. However, of their 13 patients without salivary involvement (11 with meningitis and 2 with orchitis), 7 had an elevated urinary diastase value. This relationship should be worked out more thoroughly to determine the efficacy of the values for amylase content as an aid in the diagnosis of obscure forms of mumps, particularly in relation to pancreatitis.

MENINGOENCEPHALITIS

The term meningoencephalitis is used in accordance with the American consensus in respect to all cases of mumps in which there are signs either of primary meningeal irritation with considerable pleocytosis or of primary encephalitis with a paucity of cellular elements in the spinal fluid or any combination of the two. It also includes the latent group of cases in which there is pleocytosis with no objective clinical signs of involvement of the central nervous system. This is in contrast to the use of the term made by the Scandinavians, who make a distinction between meningitis and meningoencephalitis, limiting the latter term to the less commonly encountered cases with clinical signs of severe encephalitis as well as of primary meningeal irritation.¹⁰ By making this distinction, they rightly point out the rarity of the occurrence, the more severe symptoms and signs and the increasing number of permanent sequelae seen in their "meningoencephalitic" group.

The diagnosis of clinical involvement of the central nervous system was made by the presence of the following specific symptoms and signs: severe headache, drowsiness, nausea or vomiting and stiff neck. The level of cellular abnormality of the spinal fluid was taken to be 10 cells

9. Bang, H. O., and Bang, J.: Involvement of the Central Nervous System in Mumps, *Acta med. Scandinav.* **113**:487 (April) 1943.

10. Levison, H., and Thordarson, O.: Mumps Meningitis and Meningo-Encephalitis, *Acta med. Scandinav.* **112**:312 (Oct.) 1942. Bang and Bang.⁹

recorded, giving an incidence of 1.2 per cent. This closely corresponds to the observations of Haerem,³ who found an incidence of 1 per cent in his series of 1,470 cases. The variation in these figures from those of Gellis and Peters undoubtedly represents the difference between careful personal observations and the collection of statistics from a review of clinical records.

IMMUNITY

The data from the cases in 1942 and 1943 reveal that 30 of 439 patients examined gave a history of previous infection. Of these, only 18 specified that their previous infection had been unilateral. Thus there seems to be no foundation for the general impression that the immunity gained from unilateral parotitis is not as permanent as that from bilateral salivary involvement. Three cases of recurrent parotitis were seen, the disease each time being typical of epidemic parotitis in its clinical picture and course. There was one relapse of orchitis, with a repetition of fever, swelling and pain on the same side after seven days' freedom from all symptoms or signs.

MISCELLANEOUS ENTITIES

It may seem surprising that pancreatitis is relegated to the class of miscellaneous manifestations in mumps. Yet out of 1,664 cases there were only 3 in which the symptoms and signs of pancreatitis could be observed clinically.

Considerable literature has appeared recently emphasizing the occurrence of myocarditis in mumps, although in many cases it is detectable only by electrocardiographic evidence. Only 3 cases were found in the records of the whole series in which myocardial involvement could be suspected clinically. In 1 there was sinus bradycardia without symptoms, and in 2 there was tachycardia without symptoms or abnormal electrocardiographic findings. However, Peters and Penner⁸ investigated some of the cases occurring in 1945 with routine electrocardiographic studies and found that the incidence was no higher than could be expected in any other acute infectious disease. The electrocardiographic changes were not specific for mumps.

There were 6 out of the 995 cases in 1944 in which there was some ocular involvement. The diagnoses were keratitis (2), conjunctivitis (3) and conjunctivitis and iritis (1). Treatment was given with sodium sulfathiazole in the form of eye drops or ointment, with application of pressure bandages when corneal ulceration was present.

There were only 8 cases in which bronchitis could be definitely associated with mumps. In these the condition varied in severity, but none of the patients showed any roentgenographic signs of abnormality in their chests.

8. Peters, M., and Penner, S.: *Personal communication to the author.*

No definite data were obtained on spinal fluid protein content in this large group, but in a previous experiment on the small 1945 group¹ there did seem to be a significant elevation of spinal fluid protein content in cases of both clinical and subclinical disease.

In the early part of 1945 Holden, Stevens and Eagles¹ attempted to determine the incidence of clinical and latent meningoencephalitis by doing spinal punctures routinely on the fourth day of the disease in a series of 100 patients admitted to the hospital consecutively during this same epidemic. Bang and Bang⁹ described a similar though larger series of 458 cases, involving civilians of all ages seen in the University Clinic of Epidemic Diseases in Copenhagen, in which spinal punctures were done in 371, or 85 per cent. According to the authors, the patients,

TABLE 6.—*Comparative Tables of Meningitis*

Classes	Before Adjustment			After Adjustment		
	Bang and Bang Series		Holden, Eagles and Stevens Series, Cases and per Cent	Bang and Bang Series		Holden, Eagles and Stevens Series, Cases and per Cent
	Cases	Per Cent		Cases	Per Cent	
1. Mumps without meningitis.....	126	34	63	161	43.4	63
2. Mumps with meningitis.....	245*	66	37	210	56.6	37
3. Manifest.....	106	28.6	28	97	26.1	28
4. Latent.....	129	34.5	4	94	25.3	4
5. Meningism.....	10	2.7	5	19	5.1	5
Distribution of Cases of Meningitis						
	210 cases, 100%			37 cases, 100%		
Manifest.....	46.1			75.5		
Latent.....	44.7			10.8		
Meningism.....	9.0			13.5		

* Original figures containing class 5 cases.

although admitted to a hospital for the treatment of contagious diseases, were for the most part suffering from uncomplicated mumps on admission. They divided their cases into four principal groups and designated them as follows: (1) uncomplicated cases, (2) cases with manifest meningitis (clinical signs plus pleocytosis), (3) cases with latent meningitis (pleocytosis without clinical signs) and (4) cases with meningism (clinical signs without pleocytosis). An effort has been made to compare our results from the study of a military group with those from the group of civilians of all ages studied by Bang and Bang. With utilization of information given in both articles, the results from each series were adjusted to meet similar standards for comparison. The Scandinavian classification of the types of cases was used, but the indication of pleocytosis of 3 cells per cubic millimeter was adjusted to the American standard of 10 cells. The original and the corrected figures are shown in table 6.

or more per cubic millimeter. The data obtained are summarized in table 5. Among 1,664 cases reviewed from 1942 through 1944, there were 44 with signs of meningoencephalitis. Since no specific study was being made in this group, lumbar punctures were done only as a diagnostic or therapeutic procedure, although in some they were repeated as many as three times. A total of 26 patients had spinal punctures, and in 21 of these the fluid contained at least 10 cells or more per cubic millimeter, with the maximum reaching 570 cells per cubic millimeter. Thus the incidence of clinical (proved and suspected) meningoencephalitis was 2.6 per cent in the total number of cases reviewed, while the incidence actually proved by spinal puncture was 1.26 per cent. In only 1 case was there variation from the usual predominantly lymphocytic distribution of cells. Treatment with sulfadiazine failed to have any therapeutic effect on the patient involved.

TABLE 5.—*Meningoencephalitis (1942 to 1944)**

Year (total number of cases in parentheses)	1942 (254)	1943 (415)	1944 (995)	Total Average
Number clinically suspected.....	14	8	22	44 (2.6%)
Number on which spinal punctures were done	7	2	17	26
Number in which the spinal fluid contained 10 cells or above.....	5†	2†	14†	21 (1.26%)
Fever				
Days.....	3.75	5.5	4.25	4.5
Units.....	11.75	20.5	13.6	15.28

* The average time of onset following parotitis was 4.25 days, and the range was within one day before to more than eighteen days after.

† The range was 0 to 570, and in cases in which the content was less than 10 cells the numbers were 0, 0, 2, 4 and 7.

The average time of onset of signs of meningeal involvement was 4.25 days following the appearance of the salivary swelling. Of the 995 cases observed in 1944, there were 2 in which meningeal signs preceded the parotitis and 2 in which there was no involvement of salivary glands at all. These types have been reported in several instances in the American and Scandinavian literature, and I have encountered at least 4 cases of primary meningoencephalitis without salivary swelling in which there was the confirmatory evidence of positive reactions to complement fixation tests. Fever is practically always present with signs of meningoencephalitis—so often that when it is lacking the existence of that manifestation is usually doubted unless there is an accompanying pleocytosis.

The spinal fluid pressure was elevated in many of the patients in this series, and decided relief from the severe headache, nausea and vomiting usually was obtained when as much as 15 cc. of spinal fluid was removed. The fever continues to run its usual course, however, with no correlation with the number of punctures performed or the amount of pressure relieved.

epidemic, however, there did seem to be a progressive increase in virulence of the disease as the epidemic persisted. This was manifested by the increase in the units of fever with the salivary involvement, the increasing incidence of orchitis and the increasing number of days of hospitalization for those with involvement other than that of the salivary glands.

Of the 1,664 cases reviewed, epididymo-orchitis occurred in 25.54 per cent, clinical meningoencephalitis in 2.6 per cent and presternal edema in 1.2 per cent. Pancreatitis was seen in only 3 cases, questionable myocarditis in 3 and ocular infections in 6.

A comparison of reports of involvement of the central nervous system in separate epidemics in military and civilian personnel reveals that the clinical manifestations of meningoencephalitis are found in approximately the same numbers in each class of patients when this complication is specifically searched for.

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The total number of cases of meningitis in the two series after correction is seen to be 210, or 57 per cent, for the series studied by Bang and Bang and 37 for the series of 100 cases studied by Holden, Eagles and Stevens. The numbers with manifest or clinical meningitis are found to correspond closely, with the figure for the former series being 26.1 per cent in comparison with the incidence for the latter series of 28 per cent. The number with meningism is practically the same after adjustment, being 5.1 and 5.0 per cent in the two series. The greatest discrepancy is found in the number with latent meningitis, which is 25.3 per cent in the Bang and Bang series and only 4 per cent in the other. In searching for the cause of this variation, it was discovered that Bang and Bang, in their eagerness to use only objective signs, had diagnosed manifest meningitis only in those cases in which there was definite cervical rigidity. By so doing they automatically included in the latent group all those patients with the other valid signs of involvement of the central nervous system and pleocytosis. This, then, partially accounts for the high number of patients with latent meningitis, who theoretically should have no symptoms or signs of involvement of the central nervous system. The exact incidence of the various types will probably never be determined until they are actually compared with uniform criteria for the various classes of such involvement. Despite the arguments against comparison of these two series of cases for statistical purposes the figures are strongly suggestive of certain conclusions. Sixty-one per cent of the patients in the Bang and Bang series were 14 years of age or less, and this seems to argue against Holtz's statement¹¹ that meningitis occurs more commonly among children than among adults. It also seems evident from the close correlation of the cases of clinical meningitis (with and without pleocytosis) that when there is alertness to the frequency of this manifestation it can be found in approximately equal numbers in civilian and military populations.

SUMMARY AND CONCLUSIONS

An epidemic of mumps in soldiers in which 2,500 patients were hospitalized, extending over a period of four years, was studied clinically and epidemiologically.

Mumps may be found to occur in epidemic form outside the South and Southwest whenever large groups of young nonimmune soldiers are involved.

The incidences of the various manifestations of mumps did not vary from those found in epidemics of the usual duration. In this prolonged

11. Holtz, K.: Mumpsmeningitis, *Deutsche med. Wchnschr.* **57**:536 (March 27) 1931.

easily and there occurs a local accumulation of substances to which the patient may be allergic.

Thrombosis of a vein may result in the local accumulation or trapping of quantities of an allergen sufficient to cause a local clinical allergic reaction. In an extremity in which this happens, sensitization may occur more easily as the result of slower blood flow and edema and consequent increased time of contact as well as increased quantity of allergen locally. In some allergic conditions the circulatory component may be a minor one. In the leg in which phlebitis has occurred it may be the predominant or precipitating one without which a low grade allergy might not have come to the surface or to the point of clinical manifestation. The local accumulation of sensitizing substances due to congestion has also been used to explain involvement of the butterfly area in lupus erythematosus. The rich vascularity of the flush area of the face accentuates the reaction in patients with this condition.

The concept expressed is the reverse of that in what has been called vascular allergy, in which an allergy may be the cause of the vascular disease, as, for example, in periarteritis nodosa or thromboangiitis obliterans (Rich,¹ Naide² and Thompson³). In the group of patients under discussion here, the vascular diseases thrombophlebitis and phlebothrombosis create the situation whereby allergens are trapped to bring out a subclinical allergic state or to accentuate a preexisting allergic lesion.

The sequence of events that may occur after thrombophlebitis is illustrated in the accompanying table. As the result of venous congestion, which may be due to incompetent veins as well as to thrombophlebitis, there may occur a local increase in concentration of allergens. The concentration may be to the point of clinical allergic manifestation, and a so-called stasis dermatitis or eczema develops. If there is trauma, there will be a local outpouring of these allergens into the traumatized area. This was beautifully illustrated in Auer⁴ in 1920, who demonstrated that gangrene of a rabbit's ear would occur if the rabbit were sensitized and the ear traumatized and then the sensitizing agent reinjected, whereas the untraumatized ear would remain completely unharmed. Furthermore, the local accumulation of allergens may result

1. Rich, A. R.: The Role of Hypersensitivity in Periarteritis Nodosa as Indicated by Seven Cases Developing During Serum Sickness and Sulfonamide Therapy, *Bull. Johns Hopkins Hosp.* **71**:123-140 (Sept.) 1942.

2. Naide, M.: The Causative Relationship of Dermatophytosis to Thromboangiitis Obliterans, *Am. J. M. Sc.* **202**:822-831 (Dec.) 1941.

3. Thompson, K. W.: Studies in the Relationship of Dermatophytosis to Ulceration and Gangrene of the Extremities, *Yale J. Biol. & Med.* **16**:665-853 (July) 1944.

4. Auer, J.: Local Autoinoculation of Sensitized Organisms with Foreign Protein as Cause of Abnormal Reactions, *J. Exper. Med.* **32**:427 (Oct.) 1920.

ALLERGIC LESIONS FOLLOWING THROMBOPHLEBITIS

MEYER NAIDE, M.D.

PHILADELPHIA

PATIENTS who have had thrombophlebitis and patients with varicose veins frequently have complications in the skin which have been given descriptive names such as stasis dermatitis or stasis ulcers, varicose dermatitis or varicose eczema, or postphlebitic ulcer. Despite the large incidence of stasis lesions in the legs in many patients who have varicose veins or who have had phlebitis, little is known of the underlying reasons for the development and persistence of these lesions other than that a stasis factor is present. It is customarily thought to be sufficient to say that the lesion is due to stasis.

Attention was focused on these lesions by the appearance of a large number of patients with postphlebitic and varicose ulcers who began coming to the clinic with dermatitis, severe pruritus and pain in a leg following the local use of sulfathiazole powder or ointment. The large number of such patients drew our attention to the susceptibility of the leg to sensitization or allergic reactions after the occurrence of phlebitis. We then began to observe that in patients who had had phlebitis localized allergic reactions often developed in the affected leg when no drug was used locally. For example, whenever a generalized allergic cutaneous reaction developed in a patient with a phlebitic leg, this leg would become involved first by urticaria or dermatitis and practically always was the part most affected. In several patients who were taking penicillin urticaria developed on the phlebitic leg and later on the rest of the body. Often an allergic reaction was present in the leg and nowhere else. In 1 patient who was allergic to a great many substances severe pruritus and dermatitis would at times develop on the extremity affected by phlebitis. At times this would be followed by generalized involvement of the rest of the body. If a patient who has had thrombophlebitis takes a warm bath, the involved leg may itch severely. One patient had to sit and scratch the leg after a bath. The patients often have severe itching in the affected leg when they are warm. When warm, the arteries are dilated, so that the blood is brought freely to the skin, but in legs in which there has been thrombosis of a large vein the blood cannot get out

From the Peripheral Vascular Section of the Edward B. Robinette Foundation, Medical Clinic, Hospital of the University of Pennsylvania.

often occurs. In the normal leg there usually develops little or no reaction unless the patient is highly sensitive to the adhesive tape. One of the cases reported illustrates this (case 3, figs. 3 and 4). In several patients the injection of trichophytin intracutaneously, for example, resulted in a decided reaction in the leg which had been affected with phlebitis, with a much milder reaction in the normal leg (case 2, fig. 2). The application of drugs to an extremity after the occurrence of phlebitis is likely to result in sensitization because of failure of the drug



Fig. 1 (case 1).—Dermatitis due to sensitization of sulfathiazole in an extremity in which phlebitis had occurred.

to be removed rapidly as the result of the venous thrombosis or incompetence and also probably because of previous sensitization by other antigens.

REPORT OF CASES

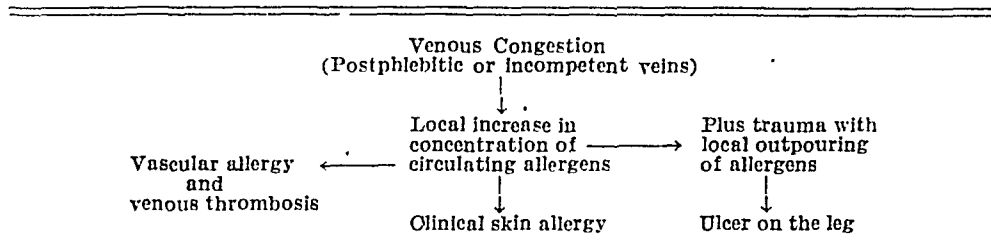
CASE 1.—H. M., a female patient, aged 38, was admitted to the Peripheral Vascular Clinic in November 1940, with a history of varicose veins for the past fifteen years and of an attack of thrombophlebitis in the left leg in 1935 following childbirth. The left leg continued swelling after the attack of phlebitis. No active treatment was carried out on her first visit to the clinic. She came

in further local vascular reactions and thrombosis and thus create a vicious cycle, so that if additional venous thrombosis takes place further venous congestion is created, with increased tendency for accumulation of allergic substances.

It is of interest that we practically never see a postphlebitic or varicose ulcer on the foot. This is probably the result of the pumping action of the foot in walking, so that stasis does not occur here.

When the lesions on a leg in which phlebitis has occurred are examined, groups of small shiny papules, or sometimes vesicles, are often seen on the skin or surrounding an ulcer. These are always associated with pruritus, so that one begins calling them "itch papules." The tops of these papules are often bloody because of previous scratching by the patient. Fluorescein was injected intravenously into a number of patients with these lesions, and the skin was examined under filtered ultraviolet radiation.⁵ The fluorescein appeared in much greater concentration in the scratched areas than in the intact skin. This was

Sequence of Events After the Occurrence of Thrombophlebitis



a visual demonstration of the concept of outpouring of allergens and other substances into traumatized areas (Auer⁴). This observation was of interest from the standpoint of a possible teleologic explanation as to why persons scratch a spot which itches. Scratching traumatizes the skin and possibly capillaries in it, so that quantities of the offending allergens escape into the traumatized skin. This may serve as a mechanism for removing the allergens from the general circulation into the skin, which is not a vital tissue. The observation with fluorescein illustrates the effect of even minor trauma on a phlebitic leg or one with varicose veins. Trauma will result in a local accumulation of allergens or bacteria in an extremity in which they are already in greater concentration than elsewhere.

One can easily demonstrate the increased sensitivity or sensitization of the leg in many patients who have had phlebitis. For example, many such patients will give a history of considerable sensitization to adhesive tape on the leg. If adhesive tape is applied, a severe reaction

5. Neller, J. L.: Use of Fluorescent Wheals in Determining Extent and Degree of Peripheral Vascular Insufficiency, *Ann. Surg.* **122**:898-901 (Nov.) 1945.

ing a kick. The leg became swollen up to the hip and blue. In 1936 ulcers developed at the site of the injection into dilated veins. In 1938 an ulcer developed on the anterior part of the right leg, which was the reason for her coming into the clinic. She complained of severe pain and swelling. On examination the entire right leg was edematous and an ulcer 2 cm. in diameter was present on the anterior surface of the right leg, with hyperpigmentation for an area 15 cm. wide completely



Fig. 3 (case 3).—Reaction of skin on leg affected by phlebitis after adhesive tape was applied for three hours; illustration of dermatitis remaining in four blocked areas one week later.

around the leg. There were a number of incompetent veins which appeared to be communicating veins. Because of a great deal of dermatophytosis at various times, the patient was tested in October 1941 with an extract of *Trichophyton purpureum* in the right leg above the pigmented area and also in the left leg. The photograph (fig. 2) illustrates the difference in reaction to the same amount of

again in February 1941 with moist dermatitis of the lower part of both legs. She was then not seen again until September 1944, when she came to the clinic with an extensive dermatitis of the left leg (fig. 1). Severe pruritus had developed, and she had then applied sulfanilamide powder, which resulted in a severe eruption due to sensitization. On examination there were a number of oozing areas on the lower part of the left leg and urticaria on the right thigh. The patient appeared to be in extreme discomfort. Three paravertebral blocks were done in the left lumbar region over a period of three weeks, after which the tenderness over the veins disappeared and the dermatitis dried up. The patient stated that the leg felt better than it had felt for years. She came to the clinic again in January 1945, with the complaint that about a week prior to admission there had developed soreness and an eruption over an area of induration on the left leg, with severe pruritus. Two days later pruritus with papillary eruption appeared over the other extremities and the trunk. The chief complaint was

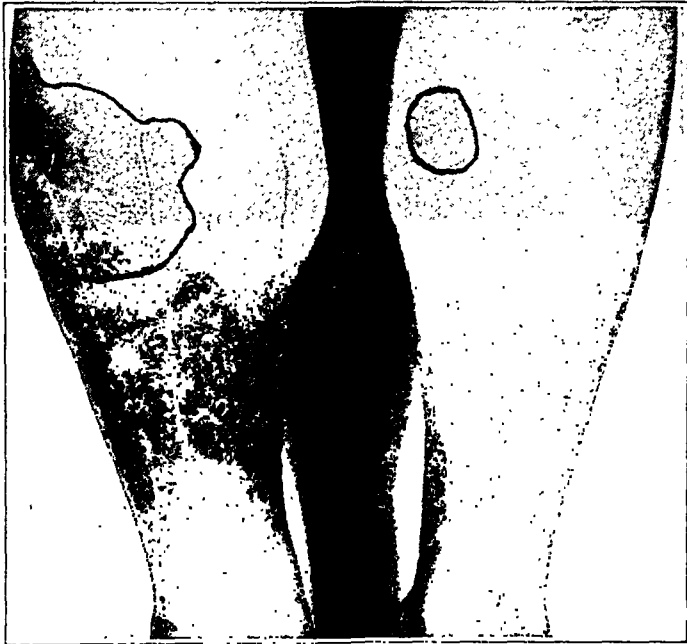


Fig. 2 (case 2).—Reaction to skin test with 0.1 cc. of extract of *Trichophyton purpureum*. There was a much greater reaction in the right leg in forty-eight hours, in which phlebitis had occurred.

pruritus, which appeared to be the result of sensitivity to an unknown allergen. There was nothing in the history to suggest the cause of the allergy. She was treated symptomatically with calamine lotion, corn starch baths, ephedrine sulfate and phenobarbital, with improvement.

This case illustrates the localization of allergic lesions in an extremity with postphlebitic involvement. With the onset of generalized pruritus and eruption, the first lesions appeared on the affected leg two days prior to involvement of the rest of the body, illustrating the tendency for greater concentration or accumulation of allergens in an area of venous congestion or the greater sensitivity of the extremity that had been affected by phlebitis.

CASE 2.—C. T., a white woman, 39 years old, was first seen in the clinic in 1938, with a history of the occurrence of phlebitis in the right leg in 1934 follow-

COMMENT

Our management of the extremity with postphlebitic involvement or of one with varicose veins with a lesion due to the stasis factor has been influenced by the concept expressed. For example, we now use cold solutions locally to cause vasoconstriction and reduce the quantity of allergens brought to the part. The patients feel better with cold applications. Rest, with elevation of the legs, has always been used in the treatment of extremities affected by phlebitis. These measures, by improving venous outflow, reduce the quantity of allergens and bacteria in the legs. The same reasoning applies to the benefit obtained from compression bandages, such as elastic stockings. Ligation of incompetent veins in the absence of major thrombosis of the deep veins often is of benefit by reducing back pressure.

Sulfonamide compounds or any other sensitizing type of drug should not be used on extremities with postphlebitic involvement, as they tend to concentrate there. Adhesive tape should never be applied directly to the skin of these extremities. Several patients have required hospitalization for several weeks as the result of having adhesive tape strapped on an ulcer, with development of a severe inflammatory reaction with edema and dermatitis on the greater part of the leg.

One of our active methods of treating the discomfort or fatigue often present in the legs of patients who have had phlebitis has been the injection of procaine hydrochloride into the lumbar sympathetic chain or ganglions. When patients began coming to the clinic with severe local reactions due to application of sulfathiazole, we were surprised to find that allergic conditions which might have been present for many months often cleared up after the injection of procaine hydrochloride into the lumbar sympathetic ganglions. This observation is being discussed in detail in a separate report.⁶

State and Wangenstein⁷ have reported intravenous injections of procaine hydrochloride as being of benefit in acute serum reactions. The reactions had resulted from the attempt to use bovine albumin in human beings as a substitute for blood during the war. The injections also cleared up the urticaria present in 6 of 7 other patients. State and Wangenstein have given a number of theories as to how procaine hydrochloride may work to relieve these allergic conditions. One of their theories is that the drug causes vasodilatation due to action on the sympathetic nervous system. The relief obtained in our group of patients was the result of injection of procaine hydrochloride into

6. Naide, M.: Treatment of Certain Dermatologic Conditions by Paravertebral Ganglion Block, *Arch. Dermat. & Syph.*, to be published.

7. State, D., and Wangenstein, O. H.: Delayed Serum Sickness, *J. A. M. A.* 130:990-995 (April 13) 1946.

trichophytin (0.1 cc.). The reaction of the right leg was severe, covering an area approximately 10 cm. in diameter, and persisted for several weeks. The reaction in the left leg was much less extensive, covering an area approximately 5 cm. in diameter, and definitely less inflammatory.

CASE 3.—M. G., a white man, 40 years old, was admitted to the clinic in November 1945, with a history of phlebitis of the left leg following a fracture twenty years previously and an incision for resetting of the displaced bone in 1943. After the operation, the incision failed to heal and an ulcer remained on the left midleg anteriorly. On examination the left calf was 43.5 cm. in circumference and the right 41 cm. There was a hyperpigmented area over the lower half of the left leg, with a necrotic ulcer 8 cm. in diameter. There was a good deal of dermatophytosis between the toes. The treatment included paravertebral blocks, local administration of tyrothricin, applications of autogenous



Fig. 4 (case 4).—After application of adhesive tape on patient's normal leg, there was no reaction.

blood, avoidance of tobacco and application of Castellani's paint. On one occasion the dressing applied to the ulcerated area was strapped down with adhesive tape, which was in contact with the skin in four places. When the patient returned to the clinic the following week, he stated that he had had to remove the adhesive tape as soon as he arrived home, three hours after its application, because of severe pruritus and discomfort. When he came in a week later the areas which were in contact with the adhesive tape were still inflamed (fig. 3). A piece of adhesive tape 2.5 cm. square was applied to the right or normal leg for three hours, during which time he had no symptoms; on removal there was no sign of any reaction (fig. 4).

This case illustrates the decided sensitivity to adhesive tape that is often present in extremities after phlebitis.

HEPATIC CIRRHOSIS AND TESTICULAR ATROPHY

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ALTHOUGH an increasing number of papers have appeared in recent years on the subject of atrophy of the testes and gynecomastia in cirrhosis of the liver, little of the work has been controlled by morphologic studies. Since atrophy and hyperplasia of tissues are to a large extent morphologic concepts, they cannot be completely evaluated without such studies. Glass, Edmondson and Soll,¹ for example, stated that of 14 males hospitalized for chronic disease of the liver there was gynecomastia in 8 and testicular atrophy in all, presumably on the basis of clinical examination. This can be deceptive, however, as the following instance will illustrate. In a recent case of active Laennec cirrhosis coming to autopsy here the combined weight of the testes was 21 Gm.; the usual weight for a man of the age of the patient is 30 to 40 Gm. It might have been supposed that well developed atrophy would be present. Yet microscopic studies showed that most of the tubules exhibited active spermatogenesis, with the production of mature sperm. In other tubules there were some early atrophic changes, which would be diagnosed as representing stage I under the terms of the scheme to be discussed later. This case is included in table 4 as an instance of active cirrhosis without atrophy. The problem should be given more attention from the morphologic standpoint. Since the changes are supposed to result from an excess of circulating estrogen, an ideal study should assess not only the weight and histologic appearance of the testes but also the condition of the prostate, seminal vesicles and breasts in men and the endometrium and breasts in women. Such an ideal study was not possible, but an attempt was made to analyze the material available.

A brief review and an abundance of references are to be found in a recent article by the Biskinds² which sums up the view that the liver normally inactivates estrogens and androgens and that in certain pathologic processes there is a selective loss of ability to inactivate estrogens. Interest in endocrine disturbances in cirrhosis of the liver was stimulated by the work of Glass, Edmondson and Soll,¹ whose bioassays of the urine

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1. Glass, S. J.; Edmondson, H. A., and Soll, S. N.: Sex Hormone Changes Associated with Liver Disease, *Endocrinology* **27**:749 (Nov.) 1940.

2. Biskind, G. R., and Biskind, M. S.: The Nutritional Aspects of Certain Endocrine Disorders, *Am. J. Clin. Path.* **16**:737 (Dec.) 1946.

the sympathetic ganglions. However, we do not know how the drug acts to relieve allergic conditions. We do not believe that vasodilatation is the chief factor in improvement of these conditions, since the patients are often made worse by complete vasodilatation when they are in a tub of warm water. Their itching and dermatitis is usually aggravated. The method of action may be that which occurs when sympathetic ganglion block with procaine hydrochloride is carried out for causalgia and may be due to interruption of a cycle of irritating stimuli set up in the extremity and in the postphlebitic lesion. It is of interest to note a report by Coca⁸ in 1944, who relieved severe gastrointestinal allergy in 6 patients by the Smithwick type of sympathectomy.

SUMMARY

The susceptibility of the extremity to allergic reactions after phlebitis is discussed. The clinical manifestations resulting from this susceptibility are described. Past thrombophlebitis or phlebothrombosis or incompetence of veins may result in trapping or accumulation of allergens as the result of venous congestion. The importance of a local circulatory factor in the localization of an allergic condition is emphasized.

Efforts to reduce arterial blood flow and also to increase venous outflow are important in treatment of allergic lesions in extremities with diseases of the veins. Removal of known allergens is important. Known sensitizing substances, such as the sulfonamide drugs, penicillin and adhesive tape, should not be used locally.

The use of paravertebral block of the regional sympathetic ganglions in treating lesions in extremities afflicted with phlebitis in the past or with varicose veins is described.

8. Coca, A. F.: Sympathectomy as an Aid in the Relief of Familial Non-reagenic Food Allergy, *Ann. Allergy* 2:213-224 (May-June) 1944.

On this basis the stage of the atrophy may be designated by a number. In stage I sperm are largely absent, spermatids may be slightly increased in number and abnormal spermatids may be present. In stage II spermatids are decreased in number and form syncytial masses and giant cells (*Spermidenriesenzellen*), and varying degrees of phagocytosis occur. In stage III the spermatocytes decrease and disappear, in stage IV the spermatogonia disappear and in stage V the Sertoli cells disappear. Obendorfer stated that occasionally sperm may persist in the tubules for a long time and even be found attached to Sertoli cells. This is rather unusual, however. In association with these changes in the character of the germinal epithelium there is a progressive diminution in the diameter of the tubules, with thickening and hyalinization of the membrana propria. To some extent the closely related stages may coexist in different tubules and even in different parts of the same tubule. The atrophic changes are often further developed near the rete testis. Nevertheless, the process with which I am here concerned is a generalized one, and I have not diagnosed as atrophic those testes which had a few small areas of completely fibrotic tubules when the remainder showed complete spermatogenesis. In addition to the changes so far described there may be an apparent or real increase in the number of Leydig cells and in their pigment content, together with a decrease in the number of interstitial connective tissue cells and varying degrees of interstitial fibrosis and hyalinization. Obendorfer briefly discusses (1) the focal atrophy and fibrosis of senility and vascular sclerosis, characteristically showing tubules with active spermatogenesis lying beside others which are completely fibrosed; (2) atrophy associated with inflammatory diseases of the testis and epididymis; (3) generalized, usually mild atrophy resulting from an increase of temperature, as in fever; (4) atrophy associated with pulmonary tuberculosis and other wasting diseases, inconstant and often focal; (5) atrophy of the tubules with great edema of the interstitial connective tissue, seen in famine edema; (6) mild generalized atrophy or suppression of spermatogenesis as a result of sexual abstinence, the data in relation to this being derived from the study of the testes of young soldiers dying in battle after several months of unrelieved front line trench warfare as compared with the testes of young civilians after sudden death; (7) atrophy associated with chronic alcoholism, which is inconstant, often focal and not definitely attributable to alcohol; (8) atrophy associated with schizophrenia and (9) atrophy associated with cirrhosis of the liver. As regards this last category, Obendorfer mentioned only the papers of Kyrle⁷ and Weichselbaum,⁸ as have other writers on the subject.

7. Kyrle, J.: Ueber Structuranomalien im menschlichen Hodenparenchym; Verhandl. d. deutsch. path. Gesellsch. **13**:391, 1909.

8. Weichselbaum, A.: Ueber Veränderungen der Hoden bei chronischem Alkoholismus, Verhandl. d. deutsch. path. Gesellsch. **14**:234, 1910.

of patients with advanced disease revealed elevated values for free estrogen, decreased values for combined estrogen and low or zero values for free androgen. Later the same investigators³ reported that after the injection of estradiol and estrone into men with cirrhosis, a high percentage could be recovered in the urine, as compared with that recovered in normal male controls. As far as the changes in the tissues are concerned, the subject has been scantily treated in the journals on pathology. Morrione⁴ has briefly reviewed what seem to be the only papers on this topic. He himself studied 28 cases of Laennec's cirrhosis and, in respect to the testes, graded the disease in 13 as "1 plus" atrophy, in 5 as "2 plus," in 9 as "3 plus" and in 1 as "no atrophy." He then chose control testes from persons of similar age groups by decades, the only other criterion of choice being absence of any disease known to predispose to testicular atrophy. After comparing the groups, he concluded that significant atrophy was present in 16 of his 28 cases and that in order to result in atrophy of the testes damage to the liver must be severe, extensive and of long standing.

The problem is approached in a somewhat different manner in the present paper. An attempt is made to correlate the testicular changes with the activity of the cirrhotic process as judged by histologic criteria. The criteria used here for diagnosing "active" cirrhosis are those set forth by Moon.⁵ The presence of Mallory bodies is the most important and constant single feature. Also indicative of activity are disintegrating parenchymal cells, active proliferation of bile ducts, infiltration by polymorphonuclear cells in areas of cell destruction and fibrous tissue, formation of new fibrous tissue and signs of parenchymal cell regeneration. Fat is not considered indicative of activity. It is usually absent in the rapidly progressing cirrhosis of childhood and varies greatly in amount in adult cirrhosis without always correlating with other signs of activity.

MORPHOLOGIC ALTERATIONS IN TESTICULAR ATROPHY

This subject is exhaustively treated by Obendorfer in the handbook of Henke and Lubarsch.⁶ Except in testicular atrophy due to roentgen irradiation, in which a selective first effect is exerted on spermatogonia and spermatocytes, with sparing of spermatids and sperm, the cells disappear in regular order of maturity, associated with certain other changes.

3. Glass, S. J.; Edmondson, H. A., and Soll, S. N.: Excretion of Estrogen After Injection of Estradiol and Estrone into Men with Cirrhosis of the Liver, *J. Clin. Endocrinol.* **4**:54 (Feb.) 1944.

4. Morrione, T. G.: Effect of Estrogens on the Testis in Hepatic Insufficiency, *Arch. Path.* **37**:39 (Jan.) 1944.

5. Moon, V. H.: Atrophic Cirrhosis, *Arch. Path.* **13**:691 (May) 1932.

6. Obendorfer, S., in Henke, F., and Lubarsch, O.: *Handbuch der speziellen pathologischen Anatomie und Histologie*, Berlin, Julius Springer, 1931, vol. 6. pt. 3, pp. 605-626.

TABLE 2.—*Inactive Laennec Cirrhosis with Testicular Atrophy*

Age of Patient, Yr.	Weight, Gm.	Liver					Testis			
		Fibrosis	Mallory Bodies	Biliary Hyperplasia	Cellular Infiltration	Fat	Germinal Epithelium	Leydig Interstitial Cells	Interstitial Fibrosis	Stage of Atrophy
57	1,015	3+	0	1+	PMN 1+ L 2+	1+	No SP No SPT Many SPC	NR	0	II
57	1,260	3+	0	2+	PMN 0 L 1+	0	No SP No SPT Few SPC	NR	0	III
76	880	4+	0	2+	PMN 0 L 2+	0	No SP No SPT Few SPC	NR	0	III
37	735	3+	0	1+	PMN 0 L 1+	0	No SP No SPT Few SPC	NR	1+	III
67	1,000	3+	0	2+	PMN 0 L 3+	0	No SP No SPT Few SPC	NR	0	III

Abbreviations: See table 1.

TABLE 3.—*Inactive Laennec Cirrhosis Without Testicular Atrophy*

Age of Patient, Yr.	Weight, Gm.	Liver					Testis			
		Fibrosis	Mallory Bodies	Biliary Hyperplasia	Cellular Infiltration	Fat	Germinal Epithelium	Leydig Interstitial Cells	Interstitial Fibrosis	Stage of Atrophy
42	1,950	3+	0	3+	PMN 0 L 3+	0	SP SPT SPC	NR	NR	No atrophy
29	2,370	1+	0	1+	PMN 0 L 2+	0	SP SPT SPC	NR	NR	No atrophy
63	1,700	2+	0	1+	PMN 0 L 2+	1+	SP SPT SPC	NR	NR	No atrophy
45	2,420	2+	0	1+	PMN 0 L 2+	2+	SP SPT SPC	NR	NR	No atrophy
59	1,620	1+	0	1+	PMN 0 L 1+	2+	SP SPT SPC	NR	NR	No atrophy
48	2,320	2+	0	1+	PMN 0 L 1+	0	SP SPT SPC	NR	NR	No atrophy
83	2,000	2+	0	1+	PMN 0 L 1+	0	SP SPT SPC	NR	NR	No atrophy
78	1,400	1+	0	1+	PMN 0 L 1+	0	SP SPT SPC	NR	NR	No atrophy
57	1,220	2+	0	2+	PMN 0 L 2+	0	SP SPT SPC	NR	NR	No atrophy
48	1,950	1+	0	1+	PMN 0 L 1+	1+	SP SPT SPC	NR	NR	No atrophy

Abbreviations: See table 1.

There seems to be little else to mention. These investigators were the first to observe the phenomenon; however, they attributed the changes to chronic alcoholism, rather than to cirrhosis.

TABLE 1.—*Active Laënnec Cirrhosis with Testicular Atrophy*

Age of Patient, Yr.	Liver						Testis			
	Weight, Gm.	Fibrosis	Mallory Bodies	Biliary Hyperplasia	Cellular Infiltration	Fat	Germinal Epithelium	Leydig Interstitial Cells	Interstitial Fibrosis	Stage of Atrophy
58	2,020	2+	1+	3+	PMN 2+ L 4+	2+	No SP No SPT Few SPO	Pigment 1+	1+	III
47	2,410	2+	1+	3+	PMN 2+ L 4+	3+	No SP No SPT Few SPO	NR	NR	III
63	1,720	3+	1+	2+	PMN 0 L 2+	2+	No SP No SPT Few SPO	Pigment 1+	NR	III
51	1,460	3+	Autolysis ?	2+	PMN 0 L 2+	2+	Autolysis No SP No SPT	NR	1+	II
45	1,720	2+	2+	2+	PMN 2+ L 4+	2+	No SP No SPT Many SPO	Pigment 1+	NR	II
41	2,460	2+	1+	2+	PMN 2+ L 4+	2+	No SP No SPT Many SPO	NR	NR	II
35	2,460	3+	1+	3+	PMN 1+ L 3+	3+	No SP No SPT Many SPO	Hyperplasia	NR	II
62	3,430	2+	1+	2+	PMN 1+ L 3+	3+	No SP No SPT Many SPO	NR	3+	II
67	2,210	2+	2+	2+	PMN 1+ L 3+	3+	No SP No SPT Few SPO	NR	NR	III
54	2,050	1+	2+	2+	PMN 2+ L 4+	2+	No SP No SPT Few SPO	NR	NR	III
52	1,565	1+	3+	2+	PMN 2+ L 4+	1+	No SP No SPT Few SPO	NR	NR	III
43	4,100	1+	2+	2+	PMN 0 L 1+	3+	No SP No SPT Many SPO	Hyperplasia	NR	II
53	2,400	2+	Autolysis ?	2+	PMN 1+ L 2+	2+	No SP No SPT Many SPO	NR	3+	II
52	2,040	1+	3+	2+	PMN 1+ L 2+	2+	No SP No SPT Few SPO	NR	NR	III
39	1,120	2+	2+	2+	PMN 1+ L 3+	2+	No SP No SPT Few SPO	Pigment 1+	1+	III
56	1,730	2+	4+	2+	PMN 1+ L 3+	2+	No SP No SPT Few SPO	NR	1+	III
43	2,225	1+	2+	2+	PMN 1+ L 3+	1+	No SP Rare SPT Many SPO	NR	1+	II

Abbreviations: SP, sperm; SPT, spermatid; SPC, spermatocyte; NR, not remarkable; PMN, polymorphonuclear leukocytes; L, lymphocytes.

RESULTS

A high incidence of testicular atrophy was found in cirrhosis judged active by histologic criteria (tables 1 and 4). It occurred in 17 of 20 cases. Similar atrophy was found in only 5 of the 15 cases of

INCIDENCE OF TUBERCULOUS PULMONARY CAVITIES IN UNEXPECTED DEATHS INVESTIGATED AT NECROPSY

EDGAR M. MEDLAR, M.D.

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THE EPIDEMIOLOGY of tuberculosis may be investigated in four ways. The most frequent method is to determine mortality rates from information contained in death registrations. In this manner large numbers of cases may be obtained, but there are two sources of error in such data to which little attention has been given. Practically all causes of death are based on clinical and not on pathologic diagnosis, and pathologists are aware of the inaccuracies which are apt to be present in such data. Even if the clinical diagnosis of the cause of death is correct, this does not exclude the possibility that active pulmonary tuberculosis was present and that tubercle bacilli were being excreted—an important condition when the epidemiology of the disease is considered. A second procedure is the tuberculin survey, from which the rate of infection may be accurately determined and from which suggestions arise as to where to search for “contact” cases. Unfortunately, most tuberculin surveys have been limited to the period of youth, and the data obtained can be used only in connection with that period. Mass roentgen surveys of the chest is a third method which, although intended primarily for the purpose of detecting clinically active tuberculous disease, may be of value in epidemiologic studies, provided all persons in a community are included and correct interpretations of pulmonary shadows are made. Two facts should always be borne in mind in reading roentgenograms of the chest. The early tuberculous focus, speaking in terms of the pathologic process, is too small and too delicate in texture to cause a shadow on the film, and it is not often that a correct diagnosis of structurally healed tuberculosis in the so-called reinfection type of disease can be made from roentgenographic shadows. Necropsy records are a fourth source of information and are of considerable epidemiologic value. These records are seldom consulted in epidemiologic studies, probably because of their

This work was sponsored by the Hegeman Research Fund.

The data discussed in this paper were made available through the courtesy of the Medical Examiner's Office of the Borough of Manhattan.

inactive cirrhosis (tables 2 and 3). The ages in the group with active disease ranged from 35 to 67 years, averaging 51.7 years. In the group with inactive cirrhosis the range was from 29 to 83, with an average of 56.7 years. In neither series was there significant local disease of the testis or epididymis or any other condition known to predispose to testicular atrophy.

COMMENT AND CONCLUSIONS

It appears that the testicular atrophy associated with Laennec's cirrhosis occurs in the phase of histologic activity of the hepatic lesion. This atrophy associated with the active phase is not invariable (table 4), is not complete (no atrophy in stage IV or V was seen) and apparently is reversible when histologic inactivity supervenes. It may be said also that the appearance of the germinal epithelium does not always correlate with the weight of the testes. This statement is made on the basis of

TABLE 4.—Active Laennec Cirrhosis Without Testicular Atrophy

Age of Patient, Yr.	Liver						Testis			
	Weight, Gm.	Fibrosis	Mallory Bodies	Biliary Hyperplasia	Cellular Infiltration	Fat	Germinal Epithelium	Leydig Interstitial Cells	Interstitial Fibrosis	Stage of Atrophy
60	2,100	2+	2+	2+	PMN 1+ L 2+	2+	SP SPT SPC	NR	NR	No atrophy
53	900	1+	1+	1+	PMN 1+ L 2+	1+	SP SPT SPC	NR	NR	No atrophy
61	1,800	2+	3+	1+	PMN 1+ L 2+	4+	SP SPT SPC	NR	NR	No atrophy

Abbreviations: See table 1.

only 1 case, previously mentioned. In this instance (table 4, second case) there was a history of exacerbations and remissions, death finally occurring as a result of hemorrhage from an esophageal varix during a phase of renewed histologic activity of the hepatic lesion.

It is not the purpose of this paper to discuss the validity of the hypothetic endocrine disturbance generally cited as the cause of the testicular atrophy in Laennec's cirrhosis, but simply to determine to what extent and in what circumstances it occurs. However, it should be mentioned that there were no instances of gynecomastia in this series. Admittedly the search for gynecomastia has been most carefully conducted only in recent years and might have been overlooked at one time. Hyperplasia of Leydig cells was found in 2 cases (table 1). Because of the variation in the number of Leydig cells in a variety of conditions,⁹ it is difficult to weigh such a finding.

9. Warren, S., and Olshausen, K. W.: Interstitial Cell Growths of the Testicle, *Am. J. Path.* 19:307 (March) 1943.

Cavity formation was found somewhat more often in the white persons than in the Negroes, the ratio being 1.4 to 1. No cavity formation was found in persons under 20 years of age. Three fourths of the subjects with cavities were white persons over 40 years of age.

TABLE 2.—Incidence of Pulmonary Tuberculous Cavities in 294 Negroes Examined

Age	Total			Sex					
	Total	Total		Male			Female		
		Num-ber with Tuberculous Cavity	Per-centage with Tuberculous Cavity	Total	Num-ber with Tuberculous Cavity	Per-centage with Tuberculous Cavity	Total	Num-ber with Tuberculous Cavity	Per-centage with Tuberculous Cavity
Total.....	294	10	3.4	193	7	3.6	101	3	2.97
3 mos. to 9 yrs.	13	7	6
10 to 19 yrs.....	37	27	10
20 to 29 yrs.....	63	1	1.6	36	27	1	3.7
30 to 39 yrs.....	68	6	8.8	40	5	12.5	28	1	3.6
40 to 49 yrs.....	59	2	3.4	40	1	2.5	19	1	5.3
50 to 59 yrs.....	36	1	2.8	29	1	3.4	7
Over 60 yrs.....	18	14	4

TABLE 3.—Incidence of Pulmonary Tuberculous Cavities in 1,038 White Persons Examined

Age	Total			Sex					
	Total	Total		Male			Female		
		Num-ber with Tuberculous Cavity	Per-centage with Tuberculous Cavity	Total	Num-ber with Tuberculous Cavity	Per-centage with Tuberculous Cavity	Total	Num-ber with Tuberculous Cavity	Per-centage with Tuberculous Cavity
Total.....	1,038	51	4.9	790	49	6.2	248	2	0.8
3 mos. to 9 yrs.	30	20	10
10 to 19 yrs.....	27	22	5
20 to 29 yrs.....	85	1	1.2	47	38	1	2.6
30 to 39 yrs.....	132	5	3.8	78	4	5.1	54	1	1.85
40 to 49 yrs.....	234	14	5.98	183	14	7.6	51
50 to 59 yrs.....	239	16	6.7	207	16	7.7	32
Over 60 yrs.....	291	15	5.2	233	15	6.4	58

Tables 2 and 3 show the distribution of subjects according to age and sex in the different races. There was little difference in relation to sex among the Negroes. Among white persons, males exhibited cavity formation 7.7 times more often than females, or almost twice as often as Negroes. Nine of every 10 white males with cavity formation were over 40 years of age.

The causes of death as filed in the office of the Medical Examiner for the Borough of Manhattan are shown in table 4 for 61 persons.

limited number, but in them are to be found the most accurate data available relative to anatomically significant tuberculous disease. It is not sufficiently appreciated that many pathologic changes, including formation of cavities, often are recorded in the anatomic diagnosis without tuberculosis appearing as the main or even as a contributing cause of death in death registries. Data from anatomic sources of information only will be analyzed in this study.

METHOD AND MATERIAL

In the past two and one-half years I have had the privilege of examining tissues for signs of tuberculous infection in cases investigated post mortem by the Medical Examiner's Staff of the Borough of Manhattan. The investigation covered unexpected, usually sudden deaths,

TABLE 1.—*Incidence of Tuberculous Pulmonary Cavities According to Age and Race in 1,332 Persons Examined, 1944-1946*

Age	Race								
	Total	Total		White			Negro		
		Num- ber with Tuber- culous Cavity	Per- centage with Tuber- culous Cavity	Total	Num- ber with Tuber- culous Cavity	Per- centage with Tuber- culous Cavity	Total	Num- ber with Tuber- culous Cavity	Per- centage with Tuber- culous Cavity
Total.....	1,322	61	4.58	1,038	51	4.9	294	10	3.4
3 mos. to 9 yrs.	43	30	13
10 to 19 yrs.....	64	27	37
20 to 29 yrs.....	148	2	1.35	85	1	1.2	63	1	1.6
30 to 39 yrs.....	200	11	5.5	132	5	3.8	68	6	8.8
40 to 49 yrs.....	293	16	5.46	234	14	5.9	59	2	3.4
50 to 59 yrs.....	275	17	6.18	239	16	6.7	36	1	2.8
Over 60 yrs.....	309	15	4.85	291	15	5.2	18

only a few of which involved hospitalized patients. Persons with extensive pulmonary disease other than tuberculosis and bodies which showed advanced postmortem decomposition were excluded. With these exceptions, representing less than 5 per cent of the material available, each person was thoroughly studied for evidence of tuberculous infection, from one and one-half to two hours being required to complete an examination. A record of the lesions and preservation of diseased tissue for future study were made in each case. The main purpose of the study was to determine the incidence of tuberculous infection and the status of the lesions. In this report only cases in which tuberculous cavities were present in the lungs will be discussed, because from an epidemiologic standpoint these were the persons who were excreting tubercle bacilli at the time of their deaths.

A total of 1,332 persons were examined, of whom 1,038 were white and 294 were Negroes. Persons over 3 months of age were included. In this group there were 61 (4.58 per cent) with tuberculous cavities in the lungs. Table 1 shows the distribution according to age and race.

infraclavicular and one third apical in position. This coincides with the pattern of pulmonary tuberculosis commonly observed in roentgenograms of the chests of adults with clinical signs of disease. In other words, this group of 61 persons presents the typical picture of so-called reinfection tuberculosis.

Since the pulmonary tissue not involved in the tuberculous process was normal in the majority of instances, an opportunity was afforded to search for calcified parenchymal foci and for evidence of healed primary complexes. In every person examined all thoracic and abdominal lymph nodes were investigated for evidence of caseation, calcification and fibrosis. In general, it is accepted that the presence of only caseous foci in lymph nodes is evidence of a primary infection and that the presence of only calcified foci is evidence of a healed primary infection.

TABLE 6.—*Condition of Thoracic Lymph Nodes in Persons with Tuberculous Pulmonary Cavity According to Age and Race*

Age, Yr.	Condition Found in Lymph Nodes											
	Total			Caseous Foci			Calcified Foci			No Caseous or Calcified Foci		
	Total	White	Negro	Total	White	Negro	Total	White	Negro	Total	White	Negro
Total	61	51	10	16	9	7	27	25	2	18	17	1
20 to 29	2	1	1	2	1	1
30 to 39	11	5	6	5	2	3	4	2	2	2	1	1
40 to 49	16	14	2	6	4	2	4	4	..	6	6	..
50 to 59	17	16	1	2	1	1	9	9	..	6	6	..
Over 60	15	15	..	1	1	..	10	10	..	4	4	..

The condition of the lymph nodes in persons with cavity formation is presented in table 6 according to age and race. According to accepted methods of differentiating between primary and reinfection tuberculosis, 16 persons presented progressive primary tuberculosis, the youngest subject being 22 years of age and the oldest 68. Twenty-seven persons had structurally healed primary infections and had acquired a progressive new disease, the youngest subject being 33 years of age and the oldest 76. In 18 cases it was not possible to state whether a primary disease or reinfection was represented, because no evidence of caseation or calcification was observed in any node. In this group the youngest subject was 34 years of age and the oldest 81.

The difference between the races in changes in lymph nodes is apparent. Seven of the 10 Negroes had caseous nodes, whereas caseous nodes were present in only 17.6 per cent of the white persons. Calcified foci and absence of macroscopic disease in lymph nodes were found oftener in white persons.

Although each of the 61 had tuberculous cavity formation and endobronchial spread, in only 13 instances was death registered as due to tuberculosis. It is the duty of the pathologists who perform the necropsies to determine the immediate cause of death, and the cause of death as filed may be regarded as accurate. This table shows data relative to important facts in the epidemiology of tuberculosis which may be absent from death registries. It also indicates the wide range of patho-

TABLE 4.—*Causes of Death in Persons with Tuberculous Pulmonary Cavities as Recorded in the Medical Examiner's Office*

Natural causes.....	27
Tuberculosis.....	13
Neoplasm.....	3
Coronary occlusion.....	3
Lobular pneumonia.....	2
Brain abscess.....	1
Acute encephalitis.....	1
Acute endocarditis.....	1
Sickle cell anemia.....	1
Exhaustive psychosis.....	1
Generalized atherosclerosis.....	1
Traumatic deaths.....	21
Alcoholism, acute and chronic.....	7
Homocide.....	2
Suicide.....	1
Drowning.....	1
Carbon monoxide poisoning.....	1
Barbiturate poisoning.....	1

TABLE 5.—*Location of Tuberculous Pulmonary Cavities (Seventy-Seven Cavities in Sixty-One Persons)*

Upper lobes.....	67
Right lung (apical, 11; subapical, 25).....	36
Left lung (apical, 10; subapical, 21).....	31
Lower lobes (all in upper third of lobe).....	9
Right lung.....	5
Left lung.....	4
Middle lobe of the right lung (upper part of lobe).....	1

logic processes which are encountered in cases that come under the supervision of the Medical Examiner's Office. In the absence of evidence obtained by necropsy or biopsy, vital statistics are of limited value.

In the majority of the cases under discussion the tuberculous process in the lungs was rather limited in extent, the remainder of the pulmonary tissue being free from any major disease. This condition afforded an opportunity to study the location of the cavities in relation to their position within the lungs and within the respective lobes. In table 5 the location of the cavities is shown. In 87 per cent of the cases the cavities were in the upper lobe, two thirds of them being

bacilli is general rather than local. This presents one of the most difficult problems in the epidemiologic control of tuberculosis.

The attempt to separate the disease into two types, i.e., progressive primary infection and progressive disease acquired after a primary infection had healed, was only partially successful, 16 persons apparently having primary infections and 27 reinfections in adult life. In the remaining 18 persons the disease was left unclassified, although some of them did show small calcified parenchymal foci which might be regarded as healed primary lesions. I do not regard such foci as necessarily representing healed primary infections, because it is known that small lesions in endobronchial spreads of the disease may calcify. This condition was shown definitely in 1 instance in this series, in which a person had been treated on several occasions for pulmonary tuberculosis over a period of twenty years, with roentgenograms of the chest available for seventeen years. After he was killed in an automobile accident, postmortem examination showed small calcified foci in three separate areas, representing the original site of disease and in two areas in which new disease was noted in roentgenograms thirteen and seventeen years after the disease was first diagnosed. In such circumstances no reliance can be placed on calcified parenchymal lesions without calcified foci in lymph nodes in the natural path of drainage as indicative of a first or of a subsequent infection. From these postmortem studies, it is evident that it is difficult and at times impossible to determine in an adult whether progressive tuberculosis represents a first or a subsequent infection. To make this differentiation by the appearance of shadows in a roentgenogram seems not to be warranted. It appears that progressive tuberculosis may develop at any age in an adult and that the clinical differentiation between "primary" and "reinfection" disease is of academic interest rather than of practical importance. A fact that is of significance in the epidemiology of the disease is that adults even in the sixth and seventh decades may contract tuberculosis and die from it.

Frequently a history of contact with a known tuberculous patient cannot be elicited from an adult with clinical tuberculosis, especially in urban areas. When a positive reaction to tuberculin occurs in a child, the home and its environs become the center of investigation in the search for "contact" cases. When clinical tuberculosis is discovered in an adult, the community as a whole should become the center of investigation for unrecognized "spreaders" of the infection. In such an investigation taverns, the eating houses, crowded places of amusement and public conveyances are of equal importance with the place of work. The data presented from this relatively small group of cases from the Medical Examiner's Office of the Borough of Manhattan indi-

COMMENT

There are many circumstances in which it is mandatory for the Medical Examiner's Office to assume jurisdiction over dead bodies. Deaths from various accidents, deaths occurring on arrival or within twenty-four hours after arrival of the patient at a hospital, homicidal and suicidal deaths and deaths occurring without the attendance of a physician all come within the scope of the Medical Examiner's jurisdiction. All the cases are handled through one office; complete post-mortem examinations are performed in all instances in which crime is suspected, in all accidental deaths in which litigation seems to be probable and in all instances in which the cause of death is obscure or unknown. Approximately 6,000 cases are handled yearly, and in about 20 per cent complete postmortem examinations are performed. It was from this material that the data presented here were obtained. The persons involved came from all parts of the Borough of Manhattan, although their legal residences may or may not have been within the Borough. Many occupations are represented. Among the persons with tuberculous cavity formation there were a garage mechanic, an elevator operator, a waiter, an accountant, a street peddler, a sailor, a truck driver and a saleslady, to mention a few. There is no "loading" of cases from the Negro district or from the indigent class. If the majority of the persons were in the lower income bracket, this condition per se was not the reason why they came under the jurisdiction of the Medical Examiner's Office, nor was it any indication that they had always been in the low income group. It is the opinion of the Medical Examiner's Office that these persons represent a fair, though small, cross section of the inhabitants of the Island of Manhattan.

It was unusual to find that the tuberculous cavity formation had been correctly diagnosed and properly treated. Of the 61 cases, in only 6 had the disease been clinically diagnosed as tuberculosis, and tuberculosis was listed as the cause of death in but 2 of the 6. In a few instances the disease was so extensive that the patients would eventually have died from it, yet tuberculosis nevertheless was not the cause of death. It would seem from these data that while mortality rates from tuberculosis are valuable they represent but one phase of the problem, which from an epidemiologic standpoint may not be as important as the detection of unrecognized spreaders of tubercle bacilli as revealed at necropsy.

The reasons for the preponderance of white men over 40 years of age with tuberculous cavities are not apparent, but there is an indication of what group of the adult population contains the greatest number of unknown spreaders of infection. If one may judge from the place of residence and type of employment, the spread of the

News and Comment

GENERAL NEWS

Mississippi Valley Medical Society.—The Twelfth Annual Meeting of the Mississippi Valley Medical Society will be held at the Municipal Auditorium, Burlington, Iowa, October 1, 2 and 3. Clinical teachers from leading medical schools will conduct the postgraduate assembly. The program is planned to appeal to general practitioners. There will be technical and scientific exhibits, a round table luncheon and a banquet preceded by a social hour. Dr. Edward L. Bortz, President of the American Medical Association, will be the principal banquet speaker, together with the presidents of the Illinois, Iowa and Missouri state medical societies. For the first time in the history of the organization, a registration fee will not be charged. All ethical physicians are cordially invited to attend. A detailed program may be obtained from the secretary, Dr. Harold Swanberg, 209-224 W. C. U. Bldg., Quincy, Ill.

Mississippi Valley Medical Society Essay Contest.—Steven O. Schwartz, M.S., M.D., and Berthe E. Armstrong, M.D., of the Hektoen Institute for Medical Research of the Cook County Hospital, Chicago, are the winners of the 1947 Mississippi Valley Medical Society Essay Contest "for the best unpublished essay on a subject of practical and applicable value to the general practitioner of medicine." Drs. Schwartz and Armstrong wrote on "Treatment of Iron Deficiency (Hypochromic Anemia)." They will receive a cash award, a gold medal and a certificate of award and will present their essay at the annual meeting in October. Their paper will appear in the January 1948 issue of the Society's official publication, the *Mississippi Valley Medical Journal*.

Mississippi Valley Medical Editors' Association.—The Fourth Annual Meeting of the Mississippi Valley Medical Editors' Association will be held at Hotel Burlington, Burlington, Iowa, Wednesday evening, October 1. A number of well known medical editors will speak. A discussion period will follow each paper. All interested in medical writing are cordially invited to attend. There will be no registration fee. A detailed program may be secured from the secretary, Harold Swanberg, M.D., 209-224 W. C. U. Bldg., Quincy, Ill.

Research Fellowships, The American College of Physicians.—The American College of Physicians announces that a limited number of fellowships in medicine will be available from July 1, 1948 to June 30, 1949. These fellowships are designed to provide an opportunity for training in research either in the basic medical sciences or in the application of these sciences to clinical investigation. They are for the benefit of physicians who are in the early stages of their preparation for a teaching and investigative career in internal medicine. Assurance must be provided that the applicant will be acceptable in the laboratory or clinic of his choice and that he will be provided with the facilities necessary for the proper pursuit of his work.

The stipend will be from \$2,200 to \$3,000. Application forms will be supplied on request to the American College of Physicians, 4200 Pine Street, Philadelphia 4,

cate the complexity of the problem of tuberculosis in the adult population. The solution of this problem requires the development of a comprehensive and realistic program of action.

SUMMARY

A study of records of 1,332 postmortem examinations from the Medical Examiner's Office of the Borough of Manhattan revealed 61 persons (4.58 per cent) with tuberculous cavities in the lungs. No tuberculous cavity was found in persons under 20 years of age. Forty-nine of the 61 persons with cavities were white males, 45 of whom were over 40 years of age. All of them presented the pattern of phthisis, i.e., so-called reinfection or adult tuberculosis with endobronchial spread. So far as it is possible to determine from postmortem examinations, the group was composed of persons with progressive primary infection, persons with progressive new infections acquired after a former infection had healed and persons with progressive disease of an indeterminate nature.

Correspondence

ERUPTIVE FEVER

To the Editor:—In the ARCHIVES (May 1947) there appeared on pages 475 and 510 two interesting articles by S. H. Soll and Wright, Gold and Jennings respectively about eruptive fever (Stevens-Johnson syndrome).

I should like to point out that in 1937 I described 2 similar cases in *Ugeskrift for læger*, page 973, which might be of interest. Unfortunately they were not published in English, so they do not appear in the résumé of cases compiled from the literature.

My cases involved two young people, a male and a female. They had generalized erythema multiforme (?) and slight pneumonia, but the most characteristic features were diffuse purulent stomatitis, severe conjunctivitis, with injection of the sclera bulbi, which were a diffuse fiery red, and purulent vulvitis and balanitis respectively.

These cases must come under group II of Soll's article, as there were severe complications.

However, there was one complication which was not mentioned in the articles in the ARCHIVES. Tuberculosis of the lungs developed in both patients in a few months after they were discharged from the hospital. I must admit that it was an accidental finding. One of the patients was admitted to the hospital for another reason, and it was then that I discovered that she had tuberculosis. I then remembered the other patient and asked him to come to see me, and I made the same discovery.

I feel that this must be a rare condition indeed, as I have never since come across any other cases of this sort, although about 40,000 patients have passed through my hands.

I have therefore been unable to ascertain if the tuberculosis which my two patients had was a coincidence or if there is any real connection between tuberculosis and this special syndrome.

W. THUNE ANDERSEN, M.D., Svendborg, Denmark.

Q FEVER

To the Editor:—Some time ago the ARCHIVES OF INTERNAL MEDICINE (76:328, 1945) published an article of mine purporting to describe an outbreak of primary atypical pneumonia observed in Italy early in 1944.

More recently, I encountered in the *American Journal of Hygiene* (44:6, July, 1946) a series of interesting studies on Q fever as it appeared among troops in and returning from Italy. A comparison of the clinical features of the cases described by Robbins and Ragan (*Am. J. Hyg.* 44:6 [July] 1946) and Feinstein and others (*ibid.* 44:72 [July] 1946) with those I published in the ARCHIVES leads me to the belief that my patients suffered from Q fever. Clinically, the rather sudden onset, early headache, duration and type of fever, paucity of physical findings in the chest, roentgenologic picture and lack of formation of cold agglutinins were characteristic of all the descriptions.

Though the matter is now largely of historic interest, for the sake of accuracy I felt that it may wisely be called to your attention and that perhaps a note should be made of it.

JACOB GROSSMAN, M.D., New York.

Montefiore Hospital for Chronic Diseases.

Pa., and must be submitted in duplicate not later than Nov. 1, 1947. Announcement of the awards will be made as promptly as possible.

The American College of Physicians Announces Its Annual Session at San Francisco, April 19 to 23, 1948.—The American College of Physicians will conduct its twenty-ninth Annual Session at San Francisco, April 19 to 23, 1948. General headquarters will be at the Civic Auditorium. Dr. William J. Kerr and Dr. Ernest H. Falconer, both of San Francisco, are the co-chairmen for local arrangements and the program of clinics and panel discussions. The President of the College, Dr. Hugh J. Morgan, Professor of Medicine at Vanderbilt University School of Medicine, Nashville, Tenn., is in charge of the program of morning lectures and afternoon general sessions.

Secretaries of medical societies are especially asked to note these dates and, in arranging meeting dates of their societies, to avoid conflicts with the meeting of the American College of Physicians, for obvious mutual benefits.

Dr. Musser's way of life was founded on two simple but enduring ideals: an unselfish desire to serve his fellows and a sincere enthusiasm for acquiring new knowledge in clinical medicine. Add to these imagina-



JOHN H. MUSSER, M.D.

1883-1947

tion, humor, gentleness of manner, tact, unmistakable honesty and integrity, and it is easy to understand why he made friends wherever he went. Physicians over the entire country grew to look on him as a

Obituaries

JOHN H. MUSSER, M.D.

1883-1947

With deep regret, the ARCHIVES announces the death of Dr. John Herr Musser at New Orleans on Sept. 5, 1947, a member of its editorial board for the past fifteen years.

Dr. Musser was the sixth John Musser in direct line to enter the profession of medicine; he seemed born and bred for a successful medical career. He was brought up in Philadelphia, graduating from the University of Pennsylvania in 1905 as a Bachelor of Science and in 1908 as a Doctor of Medicine. His promise as a teacher of clinical medicine soon was recognized so that he began his academic career early in life, finally serving from 1919 to 1924 as assistant professor of medicine at his medical school.

In 1924 he was invited to become professor of medicine at the Tulane University of Louisiana in New Orleans and here, in this chair, were spent the most productive years of his life. His clinical judgment was sound, so that his opinion was widely sought in consultation. His students appreciated the manner in which he taught: always as a clinician, not allowing theory to outweigh experience and never forgetting the personal relations that exist between physician and patient. He developed an unforeseen talent for administration; under his guidance, clinical research went forward with good teaching, so that his department soon achieved national importance both in education and in investigation.

He felt strongly the obligations of a physician as a public servant. He was a major in the Medical Corps, on active duty in France during the First World War, and he was a member of the Louisiana State Board of Health, acting as its president from 1940 to 1942.

He enjoyed writing and before he left Philadelphia was fortunate enough to acquire editorial experience through his position as assistant editor and editor of the *American Journal of Medical Sciences*. When he came to his new post, he at once took an interest in the *New Orleans Medical and Surgical Journal*, presently assuming the task of developing it and contributing to it both through original articles and through editorials. His major literary achievement, however, was the editing of his "Textbook on Internal Medicine." This appeared in 1932 and became popular immediately; in subsequent editions and reprintings it has continued to be used widely both by medical students and by practitioners.

Book Reviews

Practical Physiological Chemistry. By Philip B. Hawk, Bernard L. Oser and William H. Summerson. Twelfth edition. Price, \$10. Pp. 1323. Philadelphia: The Blakiston Company, 1946.

When a book grows to be forty years old, one of the problems it faces is how to avoid passage into a condition once described by President Theodore Roosevelt as the state of innocuous desuetude. Dr. Hawk's textbook appears to have found the answer in an entirely satisfactory manner.

In 1907, when Dr. Hawk was demonstrator of physiologic chemistry in the department of medicine at the University of Pennsylvania, he made time to write the first edition. This was before the days of the ARCHIVES, but *The Journal of the American Medical Association* reviewed the book at once. The review described it as something more than an ordinary laboratory manual and something less than a thorough treatise on physiologic chemistry. Besides giving helpful directions for mapping a systematic course in this complicated subject, it described technics and gave an intelligent discussion of recent advances in the entire field of biochemistry. It promised to be valuable not only to undergraduate students but also to clinicians and investigators.

The growth of knowledge in physiologic chemistry since then has been enormous, so that the present edition, by necessity, is three times as large as was its parent. Yet the character of the book is unchanged; in modern dress it discusses recent invasions of the field of physiology by chemistry and physics, it describes with great clarity and specificity physical and chemical laboratory methods now in use and it continues to deserve the same warm welcome which it has always received. The twelfth edition of Hawk's "Practical Physiological Chemistry" will lead a useful and popular life until the thirteenth is forthcoming.

Functional Cardiovascular Disease. By Meyer Friedman, M.D., Lt. Col., Med. Res. Corps, U. S. A.; Director, Harold Brunn Institute for Cardiovascular Research, Mt. Zion Hospital; Instructor in Medicine, Stanford Medical School, San Francisco; formerly Consultant in Medicine and Cardiologist, Tripler General Hospital, Honolulu. Cloth. Price, \$3. Pp. 266. Baltimore: Williams & Wilkins Company, 1947.

From the title one might think that this book dealt with cardiac arrhythmias, so-called functional murmurs and related topics, but this is not true. It is a full and complete exposition of the disorder known as neurocirculatory asthenia, effort syndrome, the soldier's heart and autonomic imbalance and to which perhaps are applied one or two other designations.

The author has gone thoroughly into the subject and has devoted considerable space to the different symptoms. He discusses the precordial pain, the fatigue, the breathlessness and the extracardiac pain, and he offers his explanation for these phenomena. After this he discusses the probable cause, the diagnosis and the treatment of this condition.

When one considers the tremendous amount of work that has already been done on this subject, one realizes that the author has not contributed much new material, but it is equally evident that he has not missed much of the old.

leading influence in American medicine and showed him this as best they could. They elected him president of the American College of Physicians in 1929, vice president of the American Medical Association in 1933, member of its Council on Medical Education and Hospitals in 1934, its first representative on the American Board of Internal Medicine when the Board was incorporated in 1936 and Honorary Master of the American College of Physicians in 1947, and they made him a member of such organizations as the American Society of Clinical Investigation, the Association of American Physicians, the American Clinical Climatological Association and certain smaller and more intimate interurban clinical or research clubs.

The ARCHIVES was fortunate in having Dr. Musser join its editorial board in 1932. His wisdom, his many medical contacts, his unselfishness, his enthusiasm and his honesty were as perceptible here as they were in his other fields of interest. He strove to improve the quality of the periodical so that it might continue to be of ever increasing usefulness. His influence will be lasting.

real service to medicine in producing a scholarly and authoritative compendium of knowledge in such an important field.

Pulmonary Tuberculosis. By R. Y. Keers, M.D., and B. G. Rigden, M.D. Second edition. Price, \$5. Pp. 277. Baltimore: Williams & Wilkins Company, 1947.

An ideal textbook on any subject is a difficult achievement, but the work by Dr. Keers and Dr. Rigden approaches that goal as closely as is possible in the space allowed. The authors' aims have been to restrict the size to suit the convenience of those for whom the book is intended i. e., "students and practitioners"—busy people who have no time for controversial matters or inconsequential minutiae.

On the whole, the work shows that the authors are on familiar ground throughout and have in every important discussion given the correct and most widely accepted method. The subject is discussed in the usually accepted order of sequence: bacteriology, pathology, epidemiology and resistance, diagnosis, differential diagnosis, prognosis and treatment. The latter includes, in addition to the usual methods, after-care, rehabilitation and the treatment of tuberculosis as a national problem.

It would be too much, however, to expect the book to be entirely above reproach. The dismissal of all mycoses with a short paragraph on actinomycosis may be fair enough for England, but it will not suffice for other sections of the earth, even in a limited textbook. Blastomycosis and coccidioidal infections should be mentioned, if moniliasis and histoplasmosis are not. Tularemia and brucellosis might well be considered, as well as mediastinal Hodgkin's disease, lymphosarcomas and cysts of various types. The Gaffky scale is generally thought to have outlived its usefulness, and "antiformin" (sodium hydrochlorite solution) has been abandoned long ago in sputum culturing. The new science of bronchspirometry could well have been included without adding too much to the volume of the book. The illustrations of pathologic processes are only fair, but the roentgenograms are abundant, well chosen, of good quality and well reproduced. Besides, each of the "skiagrams" has a fine companion chart to explain the abnormalities. There is no bibliography except for a few references in relation to the chapter on epidemiology and resistance.

The printing is well done, the type easy to read and the binding of the best. The book is truly all it claims to be and more.

Differential Diagnosis of Jaundice. (General Practice Manuals.) By L. Schiff, Ph.D., M.D. Price, \$5.50. Pp. 313, with 38 illustrations. Chicago: Year Book Publishers, Inc., 1946.

This little book gives an account of diseases of the liver. It is well written, sound and up-to-date and includes many references to the current periodical literature. It makes pleasant and useful reading for the physician interested in this phase of medicine.

Medical Clinics of North America. Chicago Number: Symposium on Advances in Clinical Medicine. Pp. 258, with 41 illustrations. Philadelphia: W. B. Saunders Company, 1947.

This Chicago number of the Medical Clinics of North America contains some unusually useful reviews of several current medical problems. Among these are

Patients with this condition at all times present a perplexing problem. During a war period the problem is greatly augmented. In the last war these patients were placed, to a large extent, in the care of neuropsychiatrists. Whether or not they actually belong with them is still a moot question. It is interesting to see how the author manages to stay on both sides of the fence in this question. He states frankly that he believes that all these cases have a psychiatric element. Then he seems to show in his discussion that every one has a certain nervous instability and that the victim of this disorder is merely more unstable than his fellow who shows no symptoms. Stating it in another way, it might be said that we are all a bit psychoneurotic, some of us more so than others.

The book is a carefully documented work on the subject and merits the attention of every student of cardiovascular disease.

Tuberculosis as It Comes and Goes. By Edward W. Hayes, M.D. Second edition. Price, \$3.75. Pp. 220, with 43 illustrations. Springfield, Ill.: Charles C Thomas, Publisher, 1947.

The preface of this small volume states that the book is intended for patients, but much of the material would seem to be over the heads of all but highly intellectual patients, and some material is too controversial for anyone but the specialist. Slight inaccuracies also exist with regard to the bacteriology of the disease. In addition, there is a tendency to go out of the way at times to mention certain controversial theories or discussions, as Ornstein's, Dock's and Hruby's, without mentioning other equally or more plausible theories.

There are gems for patients, however, that have been garnered from the experience of an unquestionable master of the art of treating tuberculosis. No better advice for the intellectual patient at least has ever been written. The book goes into details that only experienced physicians (and ex-patients) could know.

In addition to explanations of most phases of the disease, there are a hundred and one correct details of sanatorium life. With the assistance of Dr. de Rycke, the author has elaborated on the selection of proper mental relaxation, the supreme importance of the attitude of the mind, the role of the physician in the mental as well as physical control and what the patients' visitors should and should not do.

The illustrations are well constructed diagrams made from roentgenograms on the author's own patients and show the extent of the disease and a great variety of its complications.

The printing is done in the usual excellent manner of the publishers, the type is large and pleasing to read and the style is sufficiently smooth to make interesting "browsing" for patients and for many workers in the field of tuberculosis. The book is also to be recommended for general practitioners and even specialists who are desirous of learning more of the fine points in the treatment of this disease.

Microbial Antagonisms and Antibiotic Substances. By Selman A. Waksman. Revised edition. Price, \$4. Pp. 415. New York: The Commonwealth Fund, 1947.

Things move quickly in the domain of antibiotics, and the book of today is easily obsolete tomorrow. One welcomes, therefore, a new edition of so important a treatise as Dr. Waksman's. In this revision the number of pages has grown to 415 from 350 in the old edition; the number of references is now 1,053 instead of 1,016. Nowhere is progress more evident than in the chapter on the "chemical nature of antibiotic substances," in which appear many precise formulas not yet worked out at the time of the first edition. The Commonwealth Fund has done a

versity trustees should read, and it should be presented to public-spirited citizens who might wish to learn about modern medicine and its aspirations.

The concluding chapter discusses medical photography. Anyone will find this chapter interesting.

La silicosis pulmonar. By Hugo Dooner, M.D., with a prologue by Prof. R. Armas Cruz. Pp. 195, with 23 illustrations. Santiago de Chile: Empresa Editora Zig-Zag, S. A., 1944.

This small monograph on pulmonary silicosis is an excellent compilation of the facts on a most interesting disease. The information is garnered both from personal experiences and from an extensive review of the literature. However, there are so few physicians in the United States who can read Spanish with any degree of accuracy that it is doubtful if the book will be used by more than the limited few.

Gynäkologische Diagnostik. By Dr. Neuweiler, Professor of Gynecology and Obstetrics, University of Bern, Switzerland. Price, 58 Swiss francs. Pp. 474, with 406 illustrations. Bern, Switzerland: Hans Huber; New York: Grune & Stratton, Inc., 1946.

This comprehensive tome, for the use of general practitioners and students, devotes four hundred and seventy-four pages to the diagnosis of genitourinary diseases of women. It is the first contribution to the gynecologic textbook literature in German to come out of Switzerland since World War II. The book is written in plain and concise German. The discussions cover the broad aspects of gynecology adequately, with just enough detail to make reading easy. Print and paper are of good quality and most of the illustrations are clear and representative. The exceptions are reproductions of photomicrographs which lack definition. The arrangement of the chapters is logical, and the substance is refreshingly free from long-winded theoretic discussions. The index is rather limited, but the arrangement of individual subjects within each chapter compensates for this.

Subjects like hysterosalpingography, menstruation and its aberrations, colposcopy and backache have been treated with great thoroughness and are a distinct contribution to the literature on diagnostic procedures. Other diagnostic problems, such as the interpretation of cellular contents of vaginal deposits and endocrine dyscrasias, could have been treated more exhaustively. However, the author points out that his contribution is a *Leitfaden* (a guide) and not meant to replace general textbooks, but rather to help the general practitioner and student in organizing a proper diagnostic approach so that he may make a more logical selection of therapeutic measures. The author has relegated laboratory procedures to second place, emphasizing the ever present need for the development of a reliable clinical diagnostic acumen and leaving highly technical laboratory procedures to reference works. The book offers profitable reading for those adequately conversant with literary German.

Gastroenterology in General Practice. By Louis Pelter, M.D., with the collaboration of Louis A. Held and with contributions from Alexander Lewiston and others. Price, \$7.50. Pp. 285, with 174 illustrations. Springfield, Ill.: Charles C Thomas, 1946.

In writing this book the author has accomplished rather satisfactorily the purposes of the book discussed in the preface. The book is concise, clearly written, factual and easy to read, and it contains information of practical value, particularly to the general practitioner. The print is pleasingly clear, with large type for

the electrocardiographic studies of Katz and Weinstein, discussions of steatorrhea by Ricketts and his associates, a description by Dakin of the psychosomatic approach in general practice and a satisfactory review of information on the Rh factor by Potter. The volume contains numerous other excellent articles and is developed in a manner that should make it of great usefulness to the physician in general practice.

C-Vitaminstudier: Om korrelationerne mellem blodserumascorbinsyreindholdet, den gennem kosten indgivne C-vitaminmaengde og visse saakaldte D-hypovitaminotiske symptomer, specielt gingivitis. By Marcus Ottsen. Pp. 305. Copenhagen: Thaning and Appels Forlag, 1942.

This monograph presents studies in which a correlation is sought between the vitamin C content of the diet, the serum ascorbic acid level and the clinical conditions which might have their origin in a deficient intake of vitamin C. The subjects were 70 nurses from a municipal hospital in Copenhagen who recorded their own diets and 87 children, aged 9 to 14 years, from an asylum for feeble-minded children. Of the children, 10 were on a carefully weighed dietary, while 77 received a diet in which each meal was supervised and the number of portions ingested were recorded. The third group consisted of 249 persons whose intake of vitamin C was known approximately from "data obtained about the diet." Observations on the nurses extended over three to four weeks and those on the children three weeks.

Serum ascorbic acid content was determined by the method of Lund and Lieck, using methylene blue, and of Farmer and Abt, using 2-6 dichlorophenolindophenol. Foodstuffs when analyzed for ascorbic acid were homogenized with 10 per cent trichloroacetic acid if protein or with 10 per cent acetic acid if fruits or vegetables and centrifuged or filtered, and the clear fluid was titrated with 2-6 dichlorophenolindophenol.

The author found no specific correlation between intake of vitamin C, serum ascorbic acid level and such clinical conditions as gingivitis, bleeding of the gums or osseous changes associated with the teeth. In a group of 79 puerperal women, simple gingivitis was found to be commoner in those with serum ascorbic acid levels ranging from 0 to 0.09 mg. per hundred cubic centimeters than in those with serum ascorbic acid values of 0.10 mg. or higher.

No correlation was found to exist between the intake of vitamin C, serum ascorbic acid level and the hemoglobin content of the blood. Studies showed that there was no correlation between capillary fragility and vitamin depletion.

The latter half of the book is devoted to protocols of patients and analyses of the diets used. The tables in this section represent a great expenditure of time and effort. It apparently is assumed that the three to four week period of the disease is typical for the subject. It appears from the tables that data on some subjects were obtained during the winter and on others during the summer months. It would seem of interest to have data on the same patient collected for both seasons and preferably continuously.

Short summaries in both English and German are included.

Medical Research: A Symposium. Edited by Dr. Austin Smith. Price, \$5. Pp. 169, with 17 illustrations. Philadelphia: J. B. Lippincott Company, 1946.

This book contains eight essays which deal with medical research and its importance. Each essay is well written and is apparently designed for nonmedical rather than for professional use. This is the kind of a book that hospital or uni-

ASPERGILLOSIS AND THE ASPERGILLI

Report of a Unique Case of the Disease

EDWARD P. CAWLEY, M.D.

ANN ARBOR, MICH.

PLEBEIANS among fungi, members of the great group *Aspergillus* have attained chief notoriety as vexatious laboratory contaminants. Considerably less attention has been focused on their aptitude as instigators of disease, while their role as serviceable implements of medicine has received minimal consideration.

Aptly labeled "weeds" of the culture room,¹ over three hundred and fifty authenticated strains of aspergilli have been identified and delineated subsequent to their initial description in 1729. To warrant classification as an *Aspergillus*, a microscopic fungus must be comprised fundamentally of a stalk and a spore-bearing head. Innate minor variations occur in profusion, and though a species may be tentatively identified without undue difficulty, precise designation not infrequently entails recourse to a monograph devoted to this genus of molds exclusively.¹

The aspergilli prosper in diverse circumstances, and their ability to thrive on foodstuffs, soil and a host of seemingly barren mediums is attested to by detailed laboratory precautions often maintained for their exclusion. Though species of this mold almost invariably throttle bacteria and other fungi attempting to proliferate on the same culture medium, the morphologic response of the former in such circumstances is at times so atypical as to render identification a laborious and protracted task. Little difficulty need be anticipated in culturing and grossly classifying material from clinical sources, however, since the colony may be readily recognized as a component of this genus on the basis of its resemblance to a field of ripening grain, in which stalks and heads predominate.¹ Examination of the aerial growth under a low power of the microscope reveals details of the spore-bearing or fruiting head and other features of taxonomic significance. A preponderance of species grow best at a temperature of 37 C., although

From the Department of Dermatology and Syphilology, Medical School, University of Michigan.

1. Thom, C., and Church, M. B.: *The Aspergilli*, Baltimore, Williams & Wilkins Company, 1926.

various headings and subheadings. There are numerous illustrations which are clear and helpful. As stated by the author, this is a handbook for everyday use and not a complete reference book. As such it is subject to the same criticism that can be directed toward any book which tries to cover such a large subject in a relatively brief manner, namely, the necessity of presenting without qualifications an arbitrary, one-sided viewpoint on subjects about which there may be differences of opinion among equally competent gastroenterologists.

In instances of patients with symptoms of acute peptic ulcer, many gastroenterologists would not agree with the author's method of feeding the patient every two hours instead of every hour.

The author is to be commended for the chapters on pharmacology of the drugs affecting the autonomic nerves of the gastrointestinal tract and the psychosomatic aspects of gastrointestinal disease.

The busy practitioner will find this a handy and practical addition to his library.

Le problème des tuberculoses atypiques. By R. Burnand and others. Pp. 436, with 20 illustrations. Paris: Masson & Cie, 1946.

In his introduction, Dr. Burnand defines his subject as follows: "The atypical tuberculoses are all the incomplete or irregular pathological manifestations which, according to certain indications, principally clinical, seem to indicate an infection by the tuberculous virus but which fail to fulfill the usual criteria either anatomical or bacteriological for the diagnosis of tuberculosis." He points out that the modern desire to simplify and standardize the classification of tuberculosis has a tendency to exclude from this diagnosis all diseases or syndromes in which tubercle bacilli cannot be demonstrated in the secretions or excretions of the body. This in turn leads to ignorance of the greater portion of tuberculosis which is clinically submerged or latent.

The French schools of phthisiology and bacteriology have been for many years explorers of the difficult and shadowy fields to which this book is a guide. Here are brought together the results of studies and clinical observation by these workers in chapters written by members of the faculties of Swiss universities, principally the University of Lausanne. Burnand writes on pulmonary pathology, including epituberculosis, Loeffler's syndrome, sarcoidosis, emphysema and tuberculotoxic states. Jaeger covers the cutaneous pathologic processes of tuberculous and paratuberculous lesions of the skin. Amsler and Verrey contribute a chapter on ocular forms of tuberculosis. Tuberculous rheumatism of the type of Poncet is reviewed by Martin. The second section is devoted to the pathologic anatomy of the atypical forms of tuberculosis and is written by Nicod. The third section consists in a review of the bacteriology of non-acid-fast and filterable forms of the tubercle bacillus by Dr. P. Hauduroy.

Dr. Burnand binds the whole together with his introduction and a concluding chapter summing up the evidence for the tuberculous nature of many of these conditions. With charming frankness he says that the authors have been merely "trying to project some light into these obscurities." Much of the work referred to has been done in France, Germany and Switzerland during World War II, and hence there are few references to English or American articles in the bibliographies attached to the various chapters. Typography and paper are excellent in this paper-bound volume printed in Switzerland. Those interested in the classification of tuberculosis or in any of the conditions reviewed by the authors will find in it stimulating reading.

On the basis of these and a few other reports already available, enthusiastic prognostications as regards the future of antibiotics derived from the aspergilli appear to be well founded.

THE DISEASE ASPERGILLOSIS

Relatively few species of aspergilli have manifested pathogenicity for human beings. Perusal of available authentic data indicates that *A. fumigatus* has been isolated with greatest frequency from infections caused by the fungus, succeeded rather closely by *Aspergillus niger*. *Aspergillus glaucus*, *A. flavus* and *Aspergillus nidulans* are others implicated on occasion. Of worldwide consequence, the disease has been unearthed most often in warm, damp climates, and, as with other mycoses, more males than females are affected.⁶ Aspergillosis has been disclosed in a child of 30 months and in an adult aged 77 years, though in most cases it apparently occurs in the decades of middle life. Asymptomatic infections caused by these fungi have been encountered on occasion.⁷

Pathologic alterations incited by the aspergilli are hardly unique. Microscopic scrutiny of the granulomatous lesions which eventuate reveals focal zones of necrosis containing the organism in varied stages of maturity and attended by a multifarious cellular infiltrate. Abscesses of diverse configuration and magnitude may supervene after coalescence of such lesions. Although metastatic dispersal of the fungi has not been verified in man, there is ample presumptive evidence to denote such an occurrence.

DIAGNOSIS

The reputation maintained by these fungi as frequent contaminants militates against a diagnosis of aspergillosis unless the evidence for such a conclusion is well founded and steadfast. Direct examination of suspected material may reveal filaments and spore-bearing heads. Presence of only the former, however, does not exclude this disease from the realm of diagnostic possibilities and may merely signify an oxygen supply which is inadequate for fruition. Repeated cultures of the organism in conjunction with stringent efforts to eliminate the likelihood of it being simply a contaminant are estimable and, in combination with the occurrence of fungi in biopsy specimens, of diagnostic import. The significance of immunologic reactions is equivocal. There is a paucity of precise information concerned with antibody response to

6. Conant, N. F., and others: *Manual of Clinical Mycology*, Philadelphia, W. B. Saunders Company, 1945.

7. Donaldson, J. M., Jr.; Koerth, C. J., and McCorkle, R. G.: Pulmonary Aspergillosis, *J. Lab. & Clin. Med.* **27**:740 (March) 1942.

Aspergillus fumigatus has adequately demonstrated its ability to survive prolonged temperatures as low as -12°C ., and certain of the aspergilli were, before the advent of modern refrigeration, commonly the derivation of distinctive molds on meat in storage room. Adequate oxygen tension is a prerequisite to the development of fruiting heads, though mycelium apparently proliferates under relatively anaerobic conditions. This doubtless accounts for the abundance of filamentous forms, often accompanied with chlamydospores and occasionally with bulbous terminal structures representing abortive heads, which may be discerned infiltrating the tissues in microscopic sections in cases of aspergillosis.

THE ASPERGILLI AS IMPLEMENTS OF MEDICINE

Flavicin, extracted from a strain of *Aspergillus flavus* and penicillin, both purified by the same method to an activity of 500 Oxford units per milligram, are reputedly similar in their chemical and antibiotic properties.² Another product of *A. flavus*, aspergillic acid, in contrast, to flavicin, has been shown to inhibit the growth of human strains of *Mycobacterium tuberculosis*, and suggestive evidence is presented to indicate that the mode of action of aspergillic acid can be explained on the basis of interference with the utilization of iron by the tubercle bacillus.³

Derivation of a partially purified preparation from *A. fumigatus* and the subsequent experimental study demonstrated the material to have bacteriostatic activity against *M. tuberculosis* BCG in a 1:1,400,000 dilution and bacteriocidal efficacy against the same organism in a dilution of approximately 1:700,000.⁴ The authors reporting these results were not inclined to consider animal experiments concerned with toxicity and activity of the product until preparations of greater purity were available. It was postulated that the active substance may have been allied to helvolic acid, or purified fumigacin.

Other observers have determined that the mold *Aspergillus fumigatus* Fresenius affords several crystalline metabolic products, no less than three of which possess high antibacterial activity.⁵

2. Bush, M. T.; Goth, A., and Dickinson, H. L.: Flavicin: An Antibacterial Substance Produced by an *Aspergillus Flavus*, *J. Pharmacol. & Exper. Therap.* **84**:262 (July) 1945.

3. Goth, A.: The Antitubercular Activity of Aspergillic Acid and Its Probable Mode of Action, *J. Lab. & Clin. Med.* **30**: 899 (Nov.) 1945.

4. Asheshov, I. N., and Strelitz, F.: An Antibiotic Substance Active Against *Mycobacterium Tuberculosis*, *Science* **101**:119 (Feb. 2) 1945.

5. Birkinshaw, J. H.; Bracken, A., and Raistrick, H.: Studies in the Biochemistry of Micro-Organisms: Metabolic Products of *A. Fumigatus* Fresenius. *Biochem. J.* **39**:70, 1945.

contact with birds or grains, and pneumomycoses instigated by the aspergilli have recently been dignified by their legal accession to the category of occupational diseases.¹¹ Onset of the disease is usually insidious, although it may on occasion be brusque. The course of chronic pulmonary aspergillosis may, and not infrequently does, simulate that of pulmonary tuberculosis, while the acute variety is most often reminiscent of either bronchitis or pneumonia.⁹ Varied roentgenologic patterns have been described, the early changes being at times indistinguishable from those of tuberculosis.⁹ In an aggregation of 61 patients suspected of having pulmonary tuberculosis, painstaking scrutiny of sputum disclosed aspergillosis in 1,⁸ and there appears to be general concurrence of opinion that the disease, masquerading under the guise of tuberculosis, may be more frequent than was previously suspected. The possibility of mycelial fragments retaining acid-fast stain, resulting in confusion with Koch's bacillus, is one to be borne in mind.⁸

Attention has been directed to the aspergilli as a cause of onychomycosis within recent years, a series of 13 cases having been cited in one communication.¹² Nails of both hands and feet may be involved, the clinical picture closely simulating that caused by other fungi. Greenish discoloration of the nail plate contingent on growth of the mold is at times helpful in gross differentiation. Simultaneous infection of nails with both a species of *Aspergillus* and *Trichophyton rubrum* has been reported.¹²

Protean manifestations of aspergillosis exclusive of those previously described may, on occasion, challenge the most astute clinician. Osseous involvement has been recorded, though infrequently. Subsequent to extrusion of a small foreign body from the swollen finger of a 13 year old Negro, there developed a fluctuant swelling on the back accompanied with roentgenographic evidence of destructive changes in several vertebrae and ribs. Culture of purulent material aspirated from the lesion on the back resulted in a pure growth of *A. fumigatus*.¹³ An abscess of the cerebrum instigated by a species of this genus has been encountered,¹⁴ as has also a fatal aspergillosis of the meninges.¹⁵ Dacro-

11. Coe, G. C.: Primary Bronchopulmonary Aspergillosis, an Occupational Disease, *Ann. Int. Med.* **23**:423 (Sept.) 1945.

12. Bereston, E. S., and Waring, W. S.: *Aspergillus* Infection of the Nails, *Arch. Dermat. & Syph.* **54**:552 (Nov.) 1946.

13. Shaw, F. W., and Warthen, H. J.: Aspergillosis of Bone, *South. M. J.* **29**:1070 (Nov.) 1936.

14. Just, E.: *Aspergillus* Abscess of the Cerebrum, *Mitt. a. d. Grenzgeb. d. Med. u. Chir.* **42**:540, 1931.

15. Linck, K.: Fatal *Aspergillus* Meningitis in Man, *Virchows Arch. f. path. Anat.* **304**:408, 1931.

aspergillus infections,⁶ although some authors have expressed the opinion that this fungus, in contrast to certain others designated, does not provoke the development of agglutinins.⁸ A positive cutaneous reaction to an extract or vaccine does not discriminate between mere presence of the organism within the body and its role as an instigator of disease. Successful inoculation of animals lends credence to the belief that this fungus is causing a given infection, while failure does not exclude pathogenicity in other situations and in varied circumstances.¹ Roentgenograms, especially in pulmonary aspergillosis, may furnish presumptive evidence of mycotic etiology. In essence, a forthright and indisputable diagnosis of aspergillosis may be difficult of attainment. Microscopic specimens revealing the organism in tissues, combined with repeatedly positive cultures, are adequate for practical purposes.

CLINICAL MANIFESTATIONS

There is considerable speculation as to when aspergillosis may be labeled primary and when it is engrafted on tissues previously impaired by other disease processes. Inadequately controlled diabetes, carcinomatosis, tuberculosis, bronchiectasis, sepsis, cirrhosis of the liver, dysentery, enteritis⁹ and even syphilis⁸ have been cited as predisposing factors, and a proportion of patients with bronchial asthma and allergic rhinitis are reputedly sensitive to this mold. The term primary aspergillosis would appear to be best suited for cases in which the patients acquired the condition after prolonged exposure to massive doses of the organism and are without discernible evidence of other diseases. In a preponderance of recorded cases the disease has been of the secondary variety.

Once the organism has gained a foothold in the human host, a varied clinical picture may eventuate. Otomycosis has been publicized as the most frequently encountered manifestation of aspergillosis, although there is ample corroboration for the expressed opinion that the organism thrives in the cerumen of the external auditory canal most often as an ingenuous saprophyte,¹⁰ accompanied on occasion with erythema, scaling and crusting merely as sequels to mechanical irritation.

Pulmonary aspergillosis is prone to occur, because of vocational hazard, in farmers, feed mill workers, fur cleaners utilizing rye flour for removal of grease, threshers and others having protracted and intimate

8. Wahl, E. F., and Erickson, M. J.: Primary Pulmonary Aspergillosis, *J. M. A. Georgia* 17:341 (Aug.) 1928.

9. Van Ordstrand, H. S.: Pulmonary Aspergillosis with Report of a Case, *Cleveland Clin. Quart.* 7:66 (Jan.) 1940.

10. Dodge, C. W.: *Medical Mycology*, St. Louis, C. V. Mosby Company, 1935.

putable medical entity at best, were actually examples of infection with aspergillosis.¹⁹ Chemical analyses performed in at least 2 cases labeled as instances of this type of poisoning did not reveal sufficient quantities of the chemical to warrant an etiologic relationship, and numerous investigators have noted an abundant growth of mold on wallpaper which supposedly was implicated as the source of the arsenic. Clinical manifestations on frequent occasions have been analogous to those encountered with pulmonary aspergillosis, and the green particles, supposedly arsenic, inhaled by the patients were probably in many instances the green spores of *A. fumigatus*.¹⁹

Notwithstanding the alleged efficacy of an imposing array of reputed therapeutic agents, treatment of aspergillosis is often unsatisfactory. The sulfonamide compounds and the newer antibiotics have not, so far as can be ascertained, proved especially valuable, and reliance must continue to be placed on intensive and prolonged administration of the iodides. An established diagnosis of this disease, especially as it concerns visceral cases of long standing, must entail in most instances a circumspect prognosis.

REPORT OF A CASE

B. O., a white infant, was born on July 15, 1938. No physical abnormalities were detected when the child was examined shortly after birth, but a roentgenogram of the chest at the age of two weeks demonstrated bronchopneumonia.

On Dec. 28, 1940, the child was admitted to the Pediatrics Service of the University of Michigan Hospital because of an apparently inflammatory consolidation of the medial portion of the lower lobe of the right lung, which had been manifest since resolution of the bronchopneumonia at the approximate age of six weeks. At no time had the patient been severely ill, and sulfonamide compounds by mouth had on numerous occasions effected an apparently evanescent amelioration in objective manifestations. There were no abnormal physical findings other than the area of consolidation, and the roentgenologist was of the opinion that tuberculosis, suppurative pneumonitis and pulmonary abscess could not be excluded from the realm of diagnostic possibilities. The results of laboratory studies were well within normal limits, and after two weeks of hospitalization, a course of sulfonamide drugs having been administered, the child was discharged, the film of his chest showing a moderate amount of clearing at the involved site.

By midyear of 1942 the patient had had oft repeated bouts of slight fever accompanying manifestations of a mild respiratory infection, the roentgenogram of his chest on each occasion exhibiting consolidation of the lower lobe of the right lung. One episode was associated with pleural effusion on the right side. Direct examination, culture and inoculation of the exudate into guinea pigs were not productive of etiologic clues. In August 1942 the child was readmitted to the hospital with a tender, fluctuant mass approximately the size and shape of a child's hand located at the lower costal margin in the left anterior axillary line. A roent-

19. Hay, H. R.: Arsenical Wallpaper Poisoning or Aspergillosis, *J. Trop. Med. & Hyg.* **42**:126 (May 1) 1939.

cystitis occurring in 1 patient and blepharitis in another were depicted as ophthalmic complications of aspergillus infections primary in the nose.¹⁶ Deep black pigmentation of the vaginal wall distinguished such a mycotic infection involving this portion of the reproductive tract in an 8 year old girl, and the recorders unearthed only one comparable report in the literature.¹⁷ Further illustrative of this fungus in the role of mimic was the case of a patient manifesting cervical and axillary adenopathy in combination with pulmonary pathologic symptoms who was regarded originally as being afflicted with tuberculosis, subsequently regarded as having Hodgkin's disease and ultimately proved to have aspergillosis of both lymph nodes and of the pulmonary structures.⁸ Complete occlusion of the pulmonary artery by an elongated thrombus comprised essentially of this mold has been encountered at autopsy. The filiform structure pursued smaller arteries to their terminal branches, and the walls of the vessels were perforated at numerous sites by mycelium.⁸ Aspergilli were isolated from a periceal abscess on one occasion, and lesions of the spleen, kidneys and duodenum have been described, the majority occurring in conjunction with fatal pulmonary aspergillosis.⁸ The diagnosis of primary cutaneous aspergillosis is difficult of establishment, and the condition is probably of relatively infrequent occurrence. Mycetomas have, however, been ascribed to this organism on occasion, and *A. fumigatus* has been demonstrated as a secondary invader in a gunshot wound of the chest.⁸

Discovery of aspergilli in the feces of patients with pellagra occasioned a furor in medical circles at one time. The strain isolated was productive of strong fluorescence when cultured, and it was postulated that absorption from the gastrointestinal tract of photodynamic substances evolved by these fungi might be a factor in the causation of pellagra.¹⁸ Though alluring, this theory has not received widespread recognition. As concerns the danger associated with ingestion of mold-tainted foods, it is more than probable that these fungi are the conspicuous but usually harmless cause of damage or decay, in which situation, however, they are accompanied with bacteria or other organisms which are not grossly apparent yet which may be and often are dangerous.¹ The presence of mold in such situations is interpreted, therefore, as a warning.

Evidence has been adduced within recent years which indicates that many cases of reputed arsenical wallpaper poisoning, seldom an indis-

16. Rosenvold, L. K.: Dacrocystitis and Blepharitis Due to Infection by *Aspergillus Niger*, *Am. J. Ophth.* **25**:588 (May) 1942.

17. Weinstein, L., and Lewis, R. M.: A Case of Fungus Infection of the Vagina, *Yale J. Biol. & Med.* **11**:85 (Oct.) 1938.

18. Jobling, I. W., and Arnold, L.: The Etiology of Pellagra, *J. A. M. A.* **80**:365 (Feb. 10) 1923.

a course of penicillin resulted in no notable improvement. Comprehensive laboratory studies, with exception of the cultures previously described, had been consistently noncontributory.

As a semi-invalid, the patient remained at home until January 1946, when, at the age of 7½ years, he began to have frequent episodes of dizziness, occipital headache, projectile vomiting and staggering gait. On admission to the hospital he had pneumonia of both lower lobes and demonstrable evidence of a cerebellar lesion, which was found at operation to be an abscess and from which *A. fumigatus* was again cultured. Despite intensive and protracted treatment which included administration of penicillin, various sulfonamide compounds, potassium iodide and inhalations of ethyl iodide, the child's condition became progressively worse

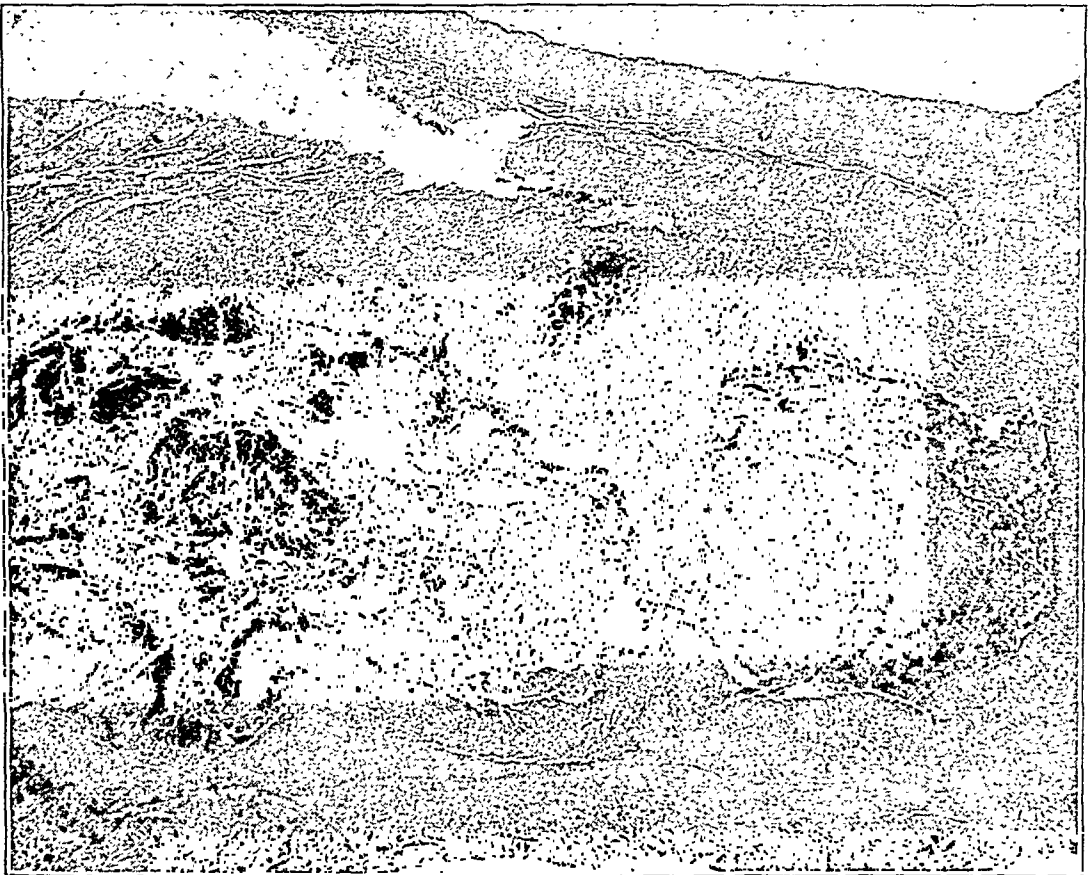


Fig. 2.—Mycotic myocardial abscesses involving the entire thickness of the wall of the left ventricle. (Low power.) The photomicrograph presented as figure 4 was made from the lesion at the left.

and recurrent abscesses, from several of which *A. fumigatus* was isolated, developed on the thoracic wall, the forehead and the right ankle. Death intervened on Sept. 6, 1946.

Complete necropsy was performed under the direction of Dr. C. V. Weller, Professor of Pathology, University of Michigan Medical School. Abscesses of variable size involving the brain, dura, heart, lungs, mediastinum, lymph nodes, spleen, liver, right kidney and right ankle were noted grossly. There was fibrino-purulent bronchitis, lobular pneumonia, obliterative fibrous pleuritis and an old perforation of the left thoracic wall, with associated abscess formation. Decubital

genogram of the chest revealed an unidentified but localized periosteal lesion involving the sternal portion of the left seventh rib and underlying the soft tissue tumor. Culture of purulent material aspirated from the lesion on two occasions resulted in the growth of a mold, subsequently identified as *A. fumigatus*.²⁰ Incision and drainage of the abscess demonstrated it to be of a multilocular structure.

At the age of 5, after two years of moderately good health, the child was found on roentgenologic examination to have pneumonia of the lower lobe of



Fig. 1.—Granulomatous foci involving the leptomeninges. These lesions contained an abundance of mycelial and filamentous structures but did not encroach on the cerebral cortex in this area. (Low power.)

the left lung, with minimal accumulation of pleural fluid at the left base. During subsequent months he had a persistent fever, the temperature ranging as high as 102 F. Administration of sulfonamide drugs appeared to be ineffective, and

20. Dr. C. W. Emmons, Principal Mycologist, United States Public Health Service, identified the organism.

in addition to relatively large myocardial and subendocardial abscesses which had ruptured into the left ventricle (fig. 2). Several of these same sites were infiltrated by variable numbers of organisms comparable to those previously described. Early coronary artery atherosclerosis was apparent.

The lungs revealed a widespread fungus-instigated pneumonitis accompanied with granulomatous masses similar to those previously described as occurring in the meninges. Mycotic abscesses were apparent in the spleen, liver, kidneys (fig. 3) and lymph nodes.

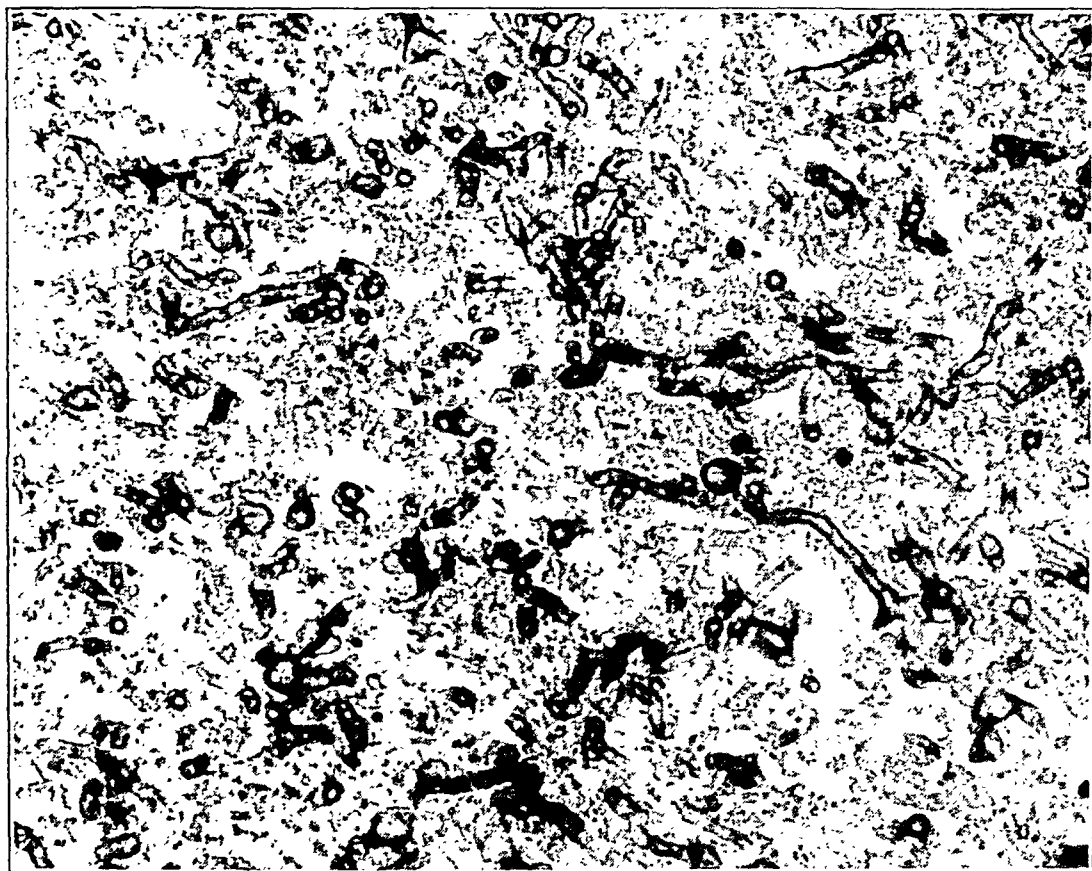


Fig. 4.—Numerous mycelial and filamentous structures, having terminal and intercalary bulbous dilatations, as they occurred in the abscesses involving the left ventricular wall. (High power.)

COMMENT

Though admittedly not verified, it would appear that this child's aspergillosis may have been implanted at the time of or shortly after birth. Indisputable, however, is the possibility that the disease was superimposed at a later date on pulmonary structures adequately prepared for such an invasion by a previously existent lesion.

Consistently normal results from laboratory studies, with the exception of cultures positive for *A. fumigatus*, were a feature of the disease process. Pneumonia, tuberculosis, suppurative pneumonitis and

ulcers were present over the sacrum and the right posterior-superior iliac region of the spine. Early generalized atherosclerosis was apparent, as was also serous atrophy of all adipose tissue. Numerous cultures inoculated from various sites were productive of a growth of *A. fumigatus*.

Subsequent microscopic changes were especially notable. The dura mater showed an organizing subacute pachymeningitis, with frequent hemosiderin-laden phagocytes, an abundance of granulation tissue and surface necrosis. In the purulent exudate were numerous mycelial and filamentous structures, possessed of terminal and intercalary bulbous dilatations. Beneath areas in which the fungus was apparent in profusion there occurred a layer of multinucleate giant cells of the Langhans type, with, in addition, abundant lipid histiocytes.



Fig. 3.—A moderately large granulomatous renal lesion. Numerous such foci were present in the kidneys, but myceliums occurred in sparse numbers. Partially destroyed glomeruli are apparent in the upper right and lower left hand corners with, in addition, a few tubules at the latter site. (Low power.)

The leptomeninges of the brain were markedly thickened, and there was an associated exudate similar to that noted in conjunction with the dura (fig. 1). An active base of granulation tissue partially limited abscessed areas containing the fungus from the brain itself, but there was patchy involvement of the cerebral cortex. Occasional foci exhibited a caseous type of necrosis. The cortex of the brain also revealed pronounced acute passive congestion and edema.

Microscopic sections of the heart showed granulomatous tissue involving the subepicardial adipose layer, the root of the aorta and the wall of the right atrium

ERYTHEMA NODOSUM

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ERYTHEMA nodosum, a disease characterized by transient nodules on the skin resembling bruises, may also be accompanied with fever and migratory arthritis. The common, mild form is usually seen and treated by dermatologists, while the severer examples are observed in hospitals, in which attention has been drawn to the systemic symptoms. It is the latter which have caused confusion over the many different conditions which may initiate erythema nodosum. Reviews of the voluminous literature on the subject¹ show how strongly entrenched the belief is that erythema nodosum is a form of either tuberculosis or rheumatic fever. Only recently has a plurality of causes been recognized and the role of hypersensitivity studied. A brief review of the obvious causes of erythema nodosum indicates how little clearcut information is available. For this reason the present clinical study has been arranged to describe the natural history of the disease. Such an approach should aid in the care of a random patient with erythema nodosum as well as improve the understanding of its complexities.

REVIEW OF THE LITERATURE

Tuberculosis.—The early observers² considered tuberculosis to be the cause of erythema nodosum. This view is still prevalent in the

From the Medical Clinic and Department of Radiology, Peter Bent Brigham Hospital, and the Department of Medicine and Radiology, Harvard Medical School.

1. (a) Wallgren, A.: Erythema Nodosum and Pulmonary Tuberculosis, *Lancet* **1**:359, 1938. (b) Ernberg, H.: Erythema Nodosum and Tuberculosis, *Am. J. Dis. Child.* **46**:1297 (Dec.) 1933. (c) Collis, W. R. F.: Erythema Nodosum, *Lancet* **2**:732, 1934. (d) Spink, W. W.: Pathogenesis of Erythema Nodosum, with Special Reference to Tuberculosis, Streptococcic Infection, and Rheumatic Fever, *Arch. Int. Med.* **59**:65 (Jan.) 1937.

2. (a) Chauffard, A., and Troisier, J.: Erythème noueux expérimentale par injection intradermique de tuberculine, *Bull. med., Paris* **27**:7, 1909. (b) Pollak, R.: Erythema Nodosum und Tuberkulose, *Wien. klin. Wchnschr.* **25**:1223, 1912. (c) Gutman, R. A.: Un cas de erythema noueux avec presence de bacilles de Koch dans le sang circulant, *Paris méé.* **21**:416, 1917. (d) Ernberg, H.: Dàs erythema nodosum, seine Natur und seine Bedeutung, *Jahrb. f. Kinderh.* **95**:1, 1921.

pulmonary abscess were the roentgenologic diagnoses which appeared to be among the most logical explanations for a pulmonary lesion which in retrospect may well have been caused by *A. fumigatus*.

Aspergillosis involving virtually every major structure of the body to a variable extent has not previously been recorded, so far as can be ascertained, and suggests hematogenous dissemination of the organism. Invasion by the mold of such structures as the myocardium and kidneys was especially remarkable.

The frequent presence of atheromatous lesions throughout the arterial tree of the bronchopulmonary system is a feature common to all types of pulmonary aspergillosis²¹ and emphasizes the probable cause of a grossly demonstrable atherosclerosis in the case reported.

SUMMARY

The aspergilli, a genus of molds, are notorious as laboratory contaminants. On rare occasion they may be the etiologic agent in production of a specific disease, and in other circumstances they may, as a source of antibiotics, function as serviceable implements of medicine.

Manifestations of the disease aspergillosis are protean, and the diagnosis may be difficult of establishment. The lungs are most frequently the site of primary involvement. Treatment is often disconcerting, there being no specific therapeutic agent.

A unique case of aspergillosis with extensive and widespread involvement of various structures is reported, accompanied with details of the gross and microscopic pathologic changes.

21. Jacobson, H. P.: *Fungous Diseases*, Springfield, Ill., Charles C Thomas, Publisher, 1932.

nodosum and rheumatic fever to streptococcic infections. For instance, it has been noted that 11 per cent of patients with erythema nodosum have preexisting rheumatic heart disease,^{1d} that migratory polyarthritides may be present in both conditions and that occasionally a prolonged P-R interval in the electrocardiogram or the new development of rheumatic murmurs has accompanied erythema nodosum.¹⁰ Undoubtedly rheumatic fever does occur with erythema nodosum, but, as we shall show, it is unusual.

Other Diseases.—Erythema nodosum is a type reaction of specific tissues to selective agents. Its frequency in any one disease has been best studied in coccidioidomycosis (5 per cent of 8,000 cases¹¹) and is similar to that observed in other infections (tuberculosis, 2 in 66 patients,¹² and streptococcic infections, 2 in 272 patients¹³) in which it is a rare manifestation of the common disease. Occasionally, syphilis,¹⁴ lymphopathia venereum,¹⁵ meningococcemia,¹⁶ influenza,¹⁷ measles,¹⁸ dental infections¹⁹ and chronic ulcerative colitis²⁰ have been accompanied with erythema nodosum.

Drugs.—Of interest because of the light shed on the pathogenesis of the disease is the ability of certain drugs to induce erythema nodosum.

10. (a) Mackenzie, S.: On Erythema Nodosum, Especially Dealing with Its Connection with Rheumatism, Tr. Clin. Soc. London **19**:215, 1886. (b) Holmes, A. H.: Erythema Nodosum, Lancet **2**:784, 1934. (c) Claman, I. A.: Erythema Nodosum: A Link in a Rheumatic Syndrome, Am. J. Dis. Child. **48**:1448 (Dec.) 1934. (d) Markson, A.: Antistreptococcal Serum for "Rheumatic" Affections, Brit. M. J. **1**:129, 1935.

11. Smith, C. E.: Epidemiology of Acute Coccidioidomycosis with Erythema Nodosum ("San Joaquin" or "Valley Fever"), Am. J. Pub. Health **30**:600, 1940.

12. Myers, J. A.; Diehl, H. S.; Boynton, R. E., and Trach, B.: Development of Tuberculosis in Adult Life, Arch. Int. Med. **59**:1 (Jan.) 1937.

13. Pilot, I., and Davis, D. J.: Sporadic Sore Throat, J. A. M. A. **97**:1691 (Dec. 5) 1931.

14. Fischl, F.: Erythema nodosum lueticum: Spirochätenbefund und Histologie, Arch. f. Dermat. u. Syph. **129**:361, 1921.

15. Hellerström, S.: A Contribution to the Knowledge of Lymphogranuloma Inguinale, Acta dermat.-venereol., 1929, supp. 1, p. 5. Amtman, L., and Pilot, I.: Lymphogranuloma Inguinale, Arch. f. Dermat. u. Syph. **26**:868, 1932. Pilot.^{8c}

16. Master, A. M.: Meningococcemia with Endocarditis, J. A. M. A. **96**:164 (Jan. 17) 1931.

17. Boganovitch, V.: Five Cases of Post-Influenzal Erythema Nodosum, Arch. Dis. Childhood **5**:56, 1930.

18. Ernberg, H., and Gabinius, O.: Close Succession of Cases of Erythema Nodosum of Nontuberculous Pathogenesis, Am. J. Dis. Child. **57**:1012 (May) 1939. Spink.^{1d}

19. Elwell, L. B.: Erythema Nodosum and Focal Infection, Brit. M. J. **1**:974, 1935.

20. Brooke, P. A.: Erythema Nodosum-Like Lesions in Chronic Ulcerative Colitis, New England J. Med. **209**:233, 1933.

British³ and Scandinavian⁴ literature. It is founded on a limited number of objective observations. Occasionally new erythema nodes have been seen after a tuberculin test,^{2a} which nodes are indistinguishable on biopsy from spontaneous lesions.^{2d} Erythema nodosum has been observed at the time the reaction to the tuberculin test became positive in previously negative reactors.⁵ It has been seen occasionally complicating miliary tuberculosis.⁶ It has also been seen with hilar shadows in the roentgenogram of the chest,⁷ although, as we shall show, this last evidence alone is equivocal.

Streptococcic Infections.—Another sparsely documented cause of erythema nodosum is infection with beta hemolytic streptococci. In this country sporadic cases have been reported.⁸ The culture of beta hemolytic streptococci in material from the throats of patients with pharyngitis accompanying erythema nodosum⁹ and the induction of remote lesions in patients with erythema nodosum with intradermal injections of streptococcic broth filtrates^{1d} or streptococcic nucleoprotein^{8c} suggest that streptococci are nevertheless a common cause of the disease.

Rheumatic Fever.—The tendency to classify erythema nodosum with the so-called hypersensitivity diseases (rheumatic fever, rheumatic states, polyarteritis nodosa, disseminated lupus erythematosus, glomerulonephritis and allergic purpuras) has clouded the relation of erythema

3. Symes, J. O.: Significance of Erythema Nodosum, *Brit. J. Dermat.* **44**:181, 1932. Footnote 1 c.

4. (a) Löfgren, S.: Primary Pulmonary Tuberculosis with Erythema Nodosum in Connection with B. C. G. Vaccination, *Acta tuberc. Scandinav.* **19**:231, 1945. (b) Wallgren, A.: Paratuberkulose Krankheitserscheinungen, in Engel, S., and von Pirquet, C.: *Handbuch der Kindertuberkulose*, Leipzig, Georg Thieme, 1930, vol. 1, p. 809; Tubercle Bacilli in Children with Erythema Nodosum: Demonstration by Gastric Lavage, *Am. J. Dis. Child.* **41**:816 (April) 1931. (c) Rotnes, P. L.: Untersuchungen über Erythema nodosum im erwachsenen Alter, *Acta dermat.-venereol.* (supp. 3) **17**:1, 1936. (d) Ernberg.^{1b}

5. (a) Gamstedt, E.: Ueber die Tuberkulinempfindlichkeit bei Erythema nodosum vor der Eruption, *Monatschr. f. Kinderh.* **59**:111, 1933. (b) Meara, F. S., and Goodridge, M.: The Relationship Between Erythema Nodosum and Tuberculosis, with Report of a Case, *Am. J. M. Sc.* **143**:393, 1912. (c) Ernberg.^{1b}

6. Landouzy, L.: Erytheme noueux et septicémies a bacillus de Koch; *Bull. Acad. de méd., Paris* **70**:400, 1913. Weber, R. P.: Erythema Nodosum with Tuberculous Bacillaemia and Meningitis, *Brit. J. Child. Dis.* **21**:119, 1924. Gutman.^{2c} Meara and Goodridge.^{5b}

7. Ernberg, H.: Erythema Nodosum, *Nord. med. tidskr.* **4**:230, 1932; footnote 2 d.

8. (a) Stone, W. R.: Erythema Nodosum Associated with Streptococcic Fautitis, *New York M. J.* **118**:673, 1923. (b) Goldstein, H. I.: Erythema Multiforme and Erythema Nodosum with Streptococcic Sore Throat, *M. J. & Rec.* **134**:266, 1931. (c) Pilot, I.: Focal Infection and Erythema Nodosum, *J. A. M. A.* **101**:2145 (Dec. 30) 1933.

9. Stone.^{8a} Pilot.^{8c}

nodes on the shins, a clear throat, palpable cervical lymph nodes and a grade 2 systolic murmur over the precordium.

Laboratory Data.—The urine was normal. The red blood cell count was 3,830,000, the hemoglobin content 11.5 Gm., the white blood cell count 11,400 and the total protein content 7.0 Gm. per hundred cubic centimeters, with 4.1 Gm. of albumin and 2.9 Gm. of globulin. Reactions to tests with first and second strength purified protein derivative were negative. Roentgenograms made during the illness and one year later are shown in figure 1. An electrocardiogram showed left axis deviation.

A follow-up examination one year later showed a normal condition. No murmurs were present.

CASE 2.—A 37 year old housewife was admitted to the hospital on June 18, 1943, because of fever, migratory arthritis and red nodes on her shins of four weeks' duration and substernal distress for three days. As a child she had been exposed to tuberculosis in the household. A roentgenogram of her chest six years before was clear. There was no history of rheumatic fever in the family. The patient was

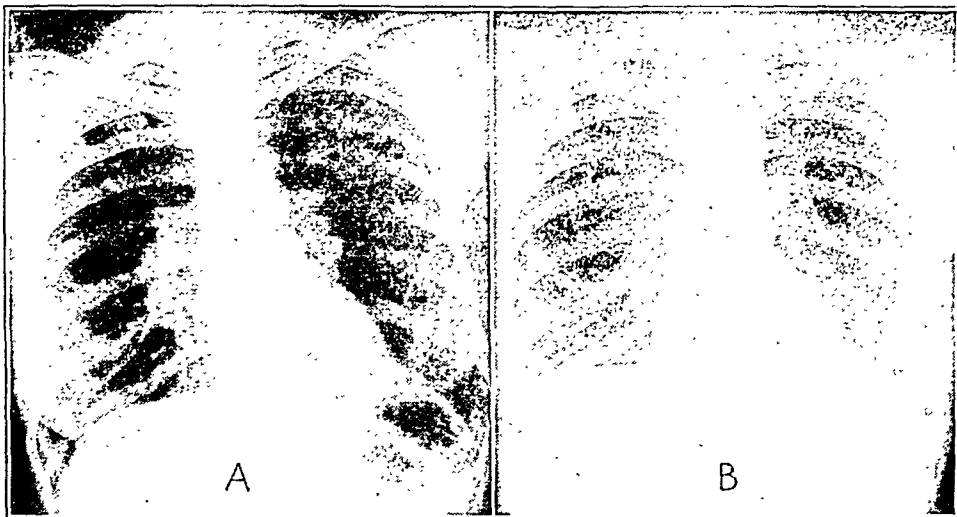


Fig. 1.—Roentgenograms in case 1. *A*, typical hilar nodes during the patient's illness. *B*, one year later.

obese, had mild angina pectoris, suffered with chronic sinusitis with postnasal discharge and had had recurrent sore throats, for which her tonsils had been removed twice.

Examination.—The temperature was 102 F., the pulse rate 120 and the respiratory rate 24. The weight was 190 pounds (86 Kg.). There were typical erythema nodes over the shins and atypical lesions on the arms. The mucous membranes of the nose and throat were injected, but no cervical adenopathy was present. The chest was clear to percussion and auscultation despite a chronic dry cough and the remarkable findings in the roentgenogram. The heart was normal.

Laboratory Data.—There was a negative reaction of the blood to the Hinton test, and the urine was clear. The red blood cell count was 4,300,000, with a hemoglobin content of 14.5 Gm. The hematocrit reading was 41. The sedimentation rate was 46 mm. in one hour (Wintrobe). The white blood cell count was 8,400, with 90 per cent polymorphonuclear cells. The total protein content was 6.4 Gm. per hundred cubic centimeters, and the fasting blood sugar content was 117 mg. The circulation time (decholin) was four seconds. The tourniquet test elicited a negative

Drugs act in two different ways. In the case of the sulfonamide compounds,²¹ they may be a provocative agent for the disease being treated. This is a similar phenomenon to that seen in primary tuberculosis, in which erythema nodosum may follow inoculation with *Bacillus Calmette-Guérin*.^{4a} The second mode of action is a primary effect of the drug itself, as, for example, erythema nodosum following iodine therapy.²²

Sarcoid.—Although the cutaneous and pulmonary lesions of erythema nodosum have been claimed to be a form of sarcoid,²³ histologic evidence obtained during an attack of erythema nodosum has not been presented, nor does the clinical course of sarcoid²⁴ conform with that described here and elsewhere²⁵ for erythema nodosum.

CLINICAL MATERIAL

The patients with erythema nodosum in this study were observed in the Peter Bent Brigham Hospital and the Children's Hospital during the past thirty years. The majority of the group and those on whom the laboratory data have been more complete have come under observation during the past ten years. Among 102 adults, 88 were women (86 per cent), and among 53 children 12 years of age or younger, 32 were girls (60 per cent). The predominance of the disease in women after the age of puberty has been noted previously²⁵ and is found also in erythema nodosum due to coccidioidomycosis.¹¹ The age at the onset of disease varied from 3 to 66 years in the present study. The majority of the patients were between 20 and 40 years of age, and 20 were over 50 years old. The following are the summaries of 2 cases studied.

CASE 1.—A 40 year old nursemaid entered the hospital on May 25, 1940, because of migratory polyarthritis and red lumps on her shins. The family history was noncontributory. At 9, 21 and 27 years of age she had isolated attacks of migratory polyarthritis. For five months she had tended a family of sickly children and had had one respiratory infection after another. Three weeks before her admission to the hospital a mild cough, sore throat and earache had developed.

Examination.—The temperature was 100.8 F., the pulse rate 90, the respiratory rate 24 and the blood pressure 108 systolic and 72 diastolic. There were typical

21. Löfgren, S.: Erythema Nodosum Following Treatment with Sulfanilamide Compounds, *Acta med. Scandinav.* **122**:175, 1945.

22. Perrin, L.: Un cas d'erytheme noueux du a l'iodure de potassium, *Marseille-med.* **29**:567, 1892.

23. Kerley, P.: (a) The Significance of the Radiological Manifestations of Erythema Nodosum, *Brit. J. Radiol.* **15**:155, 1942; (b) The Etiology of Erythema Nodosum, *ibid.* **16**:199, 1943.

24. Reisner, D.: Boeck's Sarcoid and Systemic Sarcoidosis (Besnier-Boeck-Schaumann Disease): A Study of Thirty-Five Cases, *Am. Rev. Tuberc.* **49**:289 and 437, 1944.

25. Grosse, A. H.: Erythema Nodosum: Analysis of a Hundred Cases, *Practitioner* **91**:240, 1913. Spink,^{1d} Rotnes.^{4c}

Family History.—The striking lack of rheumatic fever and tuberculosis in the detailed family histories in the hospital records is noteworthy. In the present group of 155 patients there were 15 who had a history of chorea or rheumatic heart disease in a parent, sibling, aunt or uncle. These will be discussed. Two of the 15 persons and 1 other patient in whose family there was no history of rheumatic disease also had a parent or sibling who had erythema nodosum.

Of the 155 patients, 3 gave a history of exposure to active tuberculosis and an additional 10 of exposure to tuberculosis in the household.

TABLE 1.—*Antecedent Infections in Patients with Erythema Nodosum*

	No. of Patients
Involvement of the Upper Respiratory Tract	
Pharyngitis	55
Tonsillitis	14
Peritonsillar abscess	3
Otitis media	2
"Infection of the upper respiratory tract"	16
Tonsillitis, tuberculous	1
Pharyngitis	1
Involvement of the Lower Respiratory Tract	
Sore throat, bronchitis, chest rales, low to normal white blood cell count..	11
"Grip," sore throat, conjunctivitis and scleritis.....	3
Tracheobronchitis	8
Active apical tuberculosis, with tuberculous cervical lymph nodes.....	1
Miliary tuberculosis, terminal tuberculous meningitis at autopsy.....	1
Miscellaneous	
Conjunctivitis, previous parotitis.....	1
Conjunctivitis, cervical adenopathy, mild pharyngitis, low white blood cell count	2
Infected scalp, posterior cervical adenopathy, erythema nodosum.....	1
48 hours following injection therapy with "cold vaccine" for bronchitis...	1
24 hours following passage of renal calculus.....	1
Persistent subcutaneous nodules.....	1
Erythema nodosum developing into classic ulcerative colitis.....	1
Acute gonococcic pelvic inflammatory disease.....	1
Cellulitis of the arm, axillary abscess, erythema nodosum.....	1
Abscessed teeth, erythema nodosum.....	3
Measles, sore throat, erythema nodosum.....	1
Scarlet fever, erythema nodosum.....	1

Past History.—A history of recurrent sore throats (table 1) was common. Although the respiratory infection which immediately preceded erythema nodosum often was so mild as to receive little attention from the patient or his physician, a long history of recurrent pharyngitis or chronic low grade sinusitis was more obvious. Comment is made on this point because it is in contrast to the relation between erythema nodosum and tuberculosis or coccidioidomycosis, in which erythema nodosum often accompanies the initial development of sensitivity to the infectious agent.

A past history of tuberculosis in the 155 patients was unusual. One person had a tuberculous hip as a child, while other patients who gave no known history of tuberculosis had various quiescent lesions (see roentgenograms).

reaction. The electrocardiogram contained normal curves. The roentgenogram of the chest showed the heart to be normal in size and the hilar nodes large, the node on the left being 7 cm. in diameter. In addition, there was coarse streaking in both pulmonary fields.

Course.—With rest in bed and symptomatic therapy, recovery was prompt. The cough subsided slowly. Follow-up examination of the heart and lungs and roentgenograms three years later revealed only persistent angina pectoris.

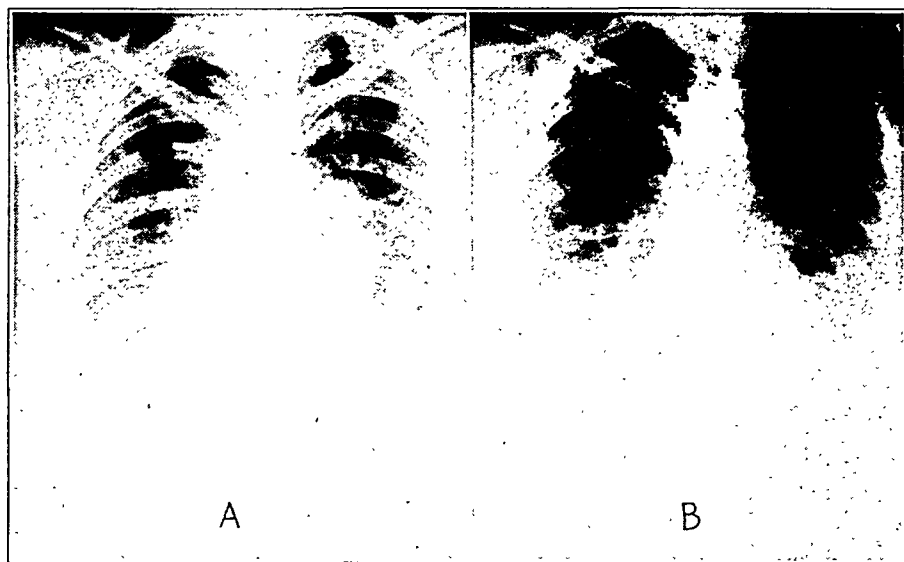


Fig. 2.—Roentgenograms in case 2. *A*, hilar nodes during the patient's illness. *B*, after recovery.

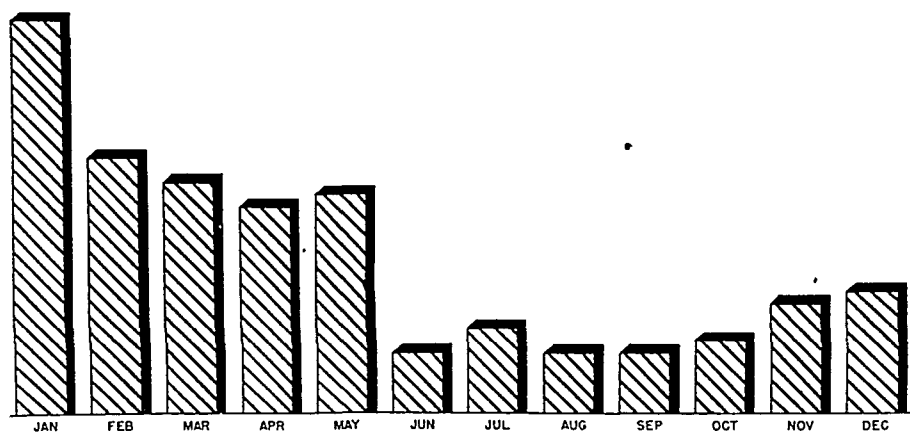


Fig. 3.—Seasonal incidence of erythema nodosum in 154 patients.

Season.—As has been noted previously,²⁵ January in particular and the winter months in general were the times when the greatest number of attacks occurred (fig. 3). In New England the peak in streptococcic infections is usually in February. In the San Joaquin Valley, where erythema nodosum is oftenest due to coccidioidomycosis, the greater number of attacks occur in the summer months.¹¹

The second child had the signs of erythema nodosum only, but tubercle bacilli were recovered from the material obtained by gastric aspiration on inoculation of a guinea pig. In the third patient, a child without history of exposure to tuberculosis, typical erythema nodosum (without pains in the joints) developed after acute tonsillitis. Tonsillectomy some weeks later unexpectedly revealed tuberculous tonsils on biopsy (table 1). In the fourth patient, a young woman also without a history of exposure, there developed erythema nodosum associated with acute cervical adenitis. Biopsy of a cervical lymph node revealed caseous tubercles, and roentgenograms of the chest demonstrated an apical infiltration, probably inactive (see section on roentgenologic findings).

Physical Examination.—The one constant physical finding was the cutaneous lesion. It began as a firm, tender, subcutaneous nodule 1 to 2 cm. in diameter. Subsequently, edema and erythema, soon followed by a bruised appearance, developed in the overlying skin. Occasionally (5 patients) there was frank nonthrombocytopenic purpura manifested by ecchymoses into the nodules and at other sites in the skin. One patient had, in addition, recurrent bleeding from the mucous membranes of the pharynx and rectum. This phenomenon is similar to that in the condition in Traut's case²⁷ which he reported as erythema nodosum with Henoch's purpura. Lesions stopped at different stages of development and regressed in the time it took them to develop. Sometimes they coalesced and seemed to fluctuate but did not suppurate. The typical lesion on the shins occasionally measured 4 to 6 cm. in diameter and lasted a week or longer. As edema subsided, a fine cigaret-paper scale often formed. In one instance of chronic ulcerative colitis, recurrent ulcerations of the nodes on the shins took place over a period of months.

Although the characteristic location of the nodules was on the vulnerable tibial and ulnar surfaces, lesions also were seen on the soles of the feet and on the calves, thighs, buttocks, upper part of the arms, scalp and face. In individual patients the site of the lesions could be directly related to local trauma. Within an hour following steady pressure of a blunt object the beginning subcutaneous nodule could be felt. A bed cradle over the legs during the night and instructions to avoid crossing the legs greatly diminished the number and severity of lesions. Extensive exposure to sunlight was not deleterious to the patient.

Arthritis.—The second most characteristic physical finding was the arthritis with the disease. Eighty of 103 adults and 13 of 53 children had pains in the joints. The ankles, knees, wrists, fingers, elbows, shoulders, hips and back, in order, were the sites involved. Pain, local

27. Traut, E. F.: Hypersensitivity in Rheumatic Disease, M. Clin. North America 18:1237, 1935.

Attacks of migratory polyarthritides lasting days to weeks, not accompanied with erythema nodosum, occurred one to twenty years before the onset of erythema nodosum in 20 of 103 adults (19 per cent) and in none of the children. Similar attacks have been observed after the onset of erythema nodosum in other patients (see account of follow-ups). The same phenomenon occurred in several of Spink's patients^{1a} and was observed by Holmes.^{10b} Of the 20 persons who had arthritis more than a year before the onset of erythema nodosum, 4 had a sore throat in association with the attack. Four others had an attack of arthritis which lasted several months. Still others of the 20 persons had two or three attacks of arthritis over a period of years, without subsequent damage to the joints or heart, and in 1 instance arthritis was accompanied with the typical perihilar lymphadenopathy of erythema nodosum but not with the cutaneous lesions. The strong similarity between the

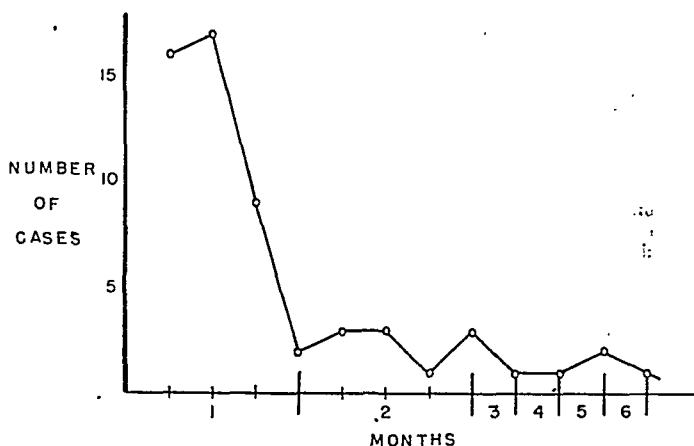


Fig. 4.—The lag between onset of infection and onset of erythema nodosum in 59 patients.

arthritis of erythema nodosum and so-called palindromic rheumatism²⁶ suggests that the latter may be a close relative to erythema nodosum.

Onset.—A known respiratory infection antedated erythema nodosum in 126, or 81 per cent, of 155 patients (table 1). The lag between the infection and the onset of erythema nodosum was usually two to four weeks (fig. 4).

In 4 of the 155 patients there was clinical evidence of active tuberculosis coincident with erythema nodosum. Two of these were children who had been exposed to the disease in the family, 1 of whom died of miliary tuberculosis six weeks after the attack of erythema nodosum.

26. Hench, P. S., and Rosenberg, E. F.: Palindromic Rheumatism: A "New," Oft Recurring Disease of Joints (Arthritis, Periarthritis, Para-Arthritis) Apparently Producing No Articular Residue; Report of Thirty-Four Cases; Its Relation to "Angioneural Arthrosis," "Allergic Rheumatism" and Rheumatoid Arthritis, *Arch. Int. Med.* **73**:293 (April) 1944.

LABORATORY OBSERVATIONS

Hemoglobin Content.—Mild secondary anemia was common. The hemoglobin content was above 13 Gm. per hundred cubic centimeters in one third of the patients, and below 10 Gm. in 15 per cent. Occasionally pronounced anemia was present.

White Blood Cell Count.—On admission of the patients to the hospital the white blood cell counts were most often normal. When pharyngitis and an elevation of temperature were present the counts usually ranged between 12,000 and 25,000, with some abnormality in the differential count. In patients with local cervical adenopathy presumably secondary to low grade pharyngitis, the white blood cell count also was frequently elevated, ranging between 11,000 and 24,000. On the other hand, the patients with infections of the lower respiratory tract, colds and grip had normal or low counts (8,800 to 1,800), with a normal differential count or with relative neutropenia.

Total Protein Content.—The total protein content was normal in 10 of the 12 patients for whom it was determined. In 4 the albumin-globulin ratios were within normal limits. In 2 others, who were tested many times, the globulin content was elevated during the acute phase of the disease, reaching 4.5 and 5.2 Gm. per hundred cubic centimeters respectively. Each of these last 2 patients had long severe illnesses, one shown to be of streptococcic origin and the other to belong to the group of infections of the lower respiratory tract.

Examination of Urine.—Transient slight albuminuria at the height of the disease was often present. Other urinary changes were not found.

Electrocardiograms.—Forty-nine out of 63 patients tested had normal tracings at various stages of their illness. Eleven patients, including 1 with hypertension and the child with acute carditis, had left axis deviation. One other patient with previously recognized rheumatic heart disease had right axis deviation. The 9 remaining persons with left axis deviation had normal hearts clinically.

Bacteriology.—Most of the bacteriologic studies were done on patients seen during the past five years. Cultures were made of material from the throat of 55 patients. No beta hemolytic streptococci were recovered from 28 persons for whom material was cultured once or from 2 for whom it was cultured twice. They were cultured one or more times in material from the remaining 25 patients. In material from several persons with recurring attacks of erythema nodosum they were cultured during attacks and could not be cultured in the intervals.

Material Used in Testing the Skin: Beta hemolytic streptococci recovered from the throats of patients with erythema nodosum or acute pharyngitis due to this organism were grown in tryptic digest broth for eighteen to forty-eight hours, washed three times by

swelling and occasionally redness and fluid were present. Often the bedridden patient had less involvement of the joints than the ambulatory patient. Arthritis before the appearance of nodes was as frequent as that appearing afterward (fig. 5).

Respiratory Infections.—The third commonest physical finding was evidence of a respiratory infection. Seventy of 155 patients had palpable cervical adenopathy—part of a recent or present infection of the throat. Nine patients had infections of the lower respiratory tract.

Heart.—Six of 155 patients were known to have rheumatic heart disease a year or more before the development of erythema nodosum. In none of these did cardiac lesions change during the present illness. Transient grade 1 or grade 2 apical systolic murmurs were heard in 50. In 6 of these the first mitral sound was also temporarily accentuated. Three other patients, children, left the hospital with suggestive systolic

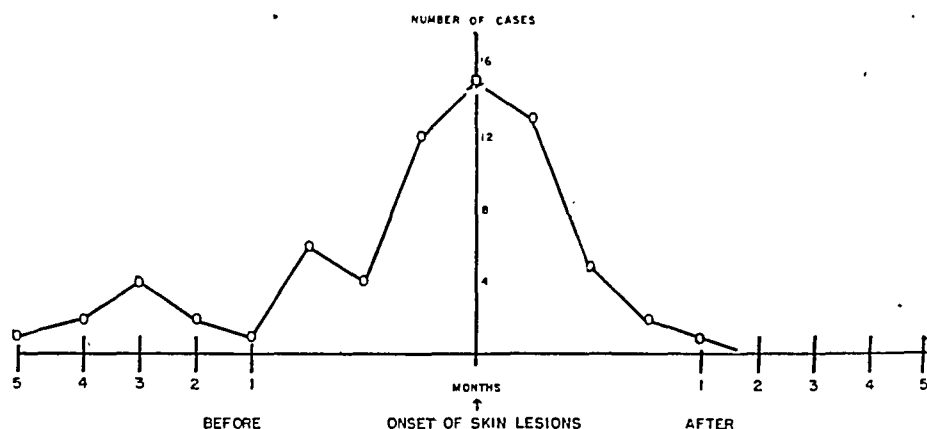


Fig. 5.—Interval between the time of arthritis and the appearance of the cutaneous lesions in 79 cases of erythema nodosum.

murmurs. Two of these had histories of rheumatic heart disease in the family and accordingly are classified as having potential rheumatic heart disease. In 1 of the 155 patients active carditis developed during the course of erythema nodosum. This was a child in whom a loud systolic and diastolic murmur developed over the precordium and who died within six weeks of acute rheumatic pancarditis (table 1). In a word, in only 1 of 155 patients did unequivocal evidence of rheumatic fever develop at the time of erythema nodosum.

Two patients had conjunctivitis and the periorbital cutaneous lesions which have been described with erythema nodosum.²⁸ Other physical abnormalities were occasionally present (table 1), but they were not a part of the clinical syndrome. It is of interest that the spleen was not palpable during the course of erythema nodosum in these patients.

28. Bluefarb, S. M., and Morris, G. E.: Erythema Nodosum of Face: Report of Case, Arch. Dermat. & Syph. 43:802 (May) 1941.

died of miliary tuberculosis, was the only one who gave a systemic reaction to tuberculin.

Pathologic Process.—A biopsy of a cutaneous node was done on 5 patients. The findings were in keeping with previously reported changes.

Roentgenologic Study.—For 65 patients roentgenograms of the chest were made during the active stage of the disease (table 2). For 37, or approximately half of the group, the findings were entirely normal in all respects. Twenty-eight had pulmonary changes, but these were nonspecific and not characteristic in two thirds of them (18 patients). They usually revealed a slight accentuation of the normal pulmonary markings, similar to that seen in any acute respiratory infection or in acute bronchitis. Two of this group had fine, diffuse mottling of both lungs similar to that seen in the earliest stages of silicosis. Three others had small areas of localized apical infiltration. In 2 these were interpreted as areas of pulmonary tuberculosis, obsolete

TABLE 2.—*Roentgenologic Examination of the Chest in Sixty-Five Patients*

Entirely negative	37
Increased fuzzy markings.....	13
Enlarged lymph nodes.....	10
Bronchial only	6
Bronchial and mediastinal.....	4
Mottling of lungs.....	2
Apical infiltration	3
Total	65

in 1, and in the other (the patient with scrofula) of questionable activity. With respect to the third patient, material obtained by gastric aspiration was sterile on inoculation of a guinea pig and reactions to cutaneous tests with first and second strength purified protein derivative were negative during the acute illness and six weeks and twelve months later. The 10 patients who had enlarged lymph nodes either at the roots of the lungs (the true bronchial nodes) or in the upper mediastinum or in both sites were the only ones who presented characteristic symptoms. In 6 of these 10 patients the enlargement was limited to the bronchial nodes and was bilateral and fairly symmetric. In 3 there was a definite clear zone between the sharply outlined, lobulated shadows of the bronchial nodes and the mediastinal shadow of the heart and great vessels. This is the only pathognomonic sign by which the enlarged nodes of erythema nodosum can be differentiated from those of other forms of lymphadenopathy. It is not always present and not always clear, but when it is present and distinct it is highly suggestive (figs. 1 and 2).

Roentgenograms of the painful swollen joints were made for several patients, and some were repeated at later examinations. None of them

centrifugation and resuspended in 0.85 per cent isotonic solution of sodium chloride, in a concentration of 1,000,000,000 organisms per cubic centimeter. The suspensions were killed by subjection to a temperature of 56 C. for thirty minutes on two successive days, with storage in the interval at 4 C., and sterility was checked by subculture in thyoglycolate mediums (Brewer). Patients were tested with 0.1 cc. of vaccine intradermally in the forearm. If a severe reaction could be anticipated from the presence of an obvious streptococcic infection, 1:10 or 1:100 dilutions were first tried.

Results: Reaction patterns were of two types, local and systemic. The local reaction consisted in induration, with an area of edema and erythema of a centimeter or more in diameter beginning often within twelve hours and usually becoming maximal in twenty-four hours. The systemic reaction usually began within five to twelve hours and consisted in increased malaise, arthralgias of the knees and ankles, at times with swelling of the joints, anorexia and sometimes a rise in the body temperature. For purposes of this study, well defined systemic reactions and/or the development of new erythema nodes following the cutaneous test were considered significant when the tests done at a different time with purified protein derivative, brucellergen, lygranum or an alpha streptococcus vaccine did not cause similar reactions.

Twenty-eight patients were studied with multiple tests of the skin. Fifteen of 17 in whom beta hemolytic streptococci were demonstrated in their throats by culture had a significant systemic reaction and an increase in nodes following the cutaneous test with beta streptococcus and not following other cutaneous tests. Eleven of the 13 other patients similarly tested gave a positive local streptococcic reaction only. Retesting 4 of the 15 patients who had had systemic reactions at a later time when their disease was mild or subsiding did not reproduce systemic reactions or nodes but did cause the local cutaneous reaction.

One patient gave a local and systemic reaction, including the appearance of new nodes, with an alpha streptococcus reaction and not with a beta hemolytic streptococcus reaction. Following extraction of two infected teeth, a febrile, incapacitating bout of erythema nodosum which had been smoldering for five months was abruptly terminated. The patient has remained well during a year of follow-up observations.

Tuberculin Tests.—Sixty-one patients were tested with purified protein derivative intradermally. Twenty-one of these were also tested with beta hemolytic streptococcus vaccine and showed a local or systemic reaction mentioned previously. Seven of the group tested with streptococcus vaccine and 22 others, or a total of 29 of the 61 patients, had positive cutaneous reactions to the first or second strength purified protein derivative. One of the 61, the patient who subsequently

the pharynx to shrink hypertrophied lymphoid tissue lengthened the asymptomatic intervals in chronic relapsing erythema nodosum. Local irrigations of the throat, artificial fever therapy (typhoid, four chills) by the method of Solomon³⁰ and administration of salicylates were nonspecific modes of therapy used, without altering the course of the disease. Two patients, ill for more than five months with persistent febrile erythema nodosum, were brought to a state in which they were free from signs and symptoms and maintained there for a year following a course of desensitization with beta hemolytic streptococcus vaccine given subcutaneously in increasing nonreacting amounts, similar to the methods used for desensitization in hay fever. Each of these patients, however, has had a later recurrence of erythema nodosum during subsequent pharyngitis caused by beta hemolytic streptococci.

Duration.—Erythema nodosum is usually a self-limited disease of one to five weeks' duration. Attacks may smolder on in a subacute stage for three to nine months and occasionally for years (5 patients). In these unfortunate persons the symptoms are periodic in intensity and rarely completely absent. Ten per cent of the 155 patients had the chronic form of the disease. In other studies^{1d} recurrence of erythema nodosum as well as a smoldering course has also been noted. In this series attacks recurred one to twenty years later (4 patients) or recurred several times at wide intervals in the same patient (6 patients).

Follow-up Examination.—A follow-up examination one year or longer after the onset of erythema nodosum was made on 61 of the 155 patients. Eleven patients gave a subsequent history of chronically recurring manifestations of erythema nodosum in the skin and joints over a period of two to ten years. Two of these persons had rheumatic heart disease, which had been recognized before the first evidence of erythema nodosum. Seven of the 61 persons, 2 of whom had rheumatic heart disease, had one or more isolated attacks of erythema nodosum following their first attack. Nine of the 61 patients had one or more bouts of arthritis without erythema nodosum at a later date. Two of these, each followed for a year, have retained a grade 2 systolic murmur, which is suggestive of early mitral disease, and in 1 patient who had a normal heart at the time of erythema nodosum rheumatic aortic insufficiency developed six years later. This last patient is the only one of the 61 in whom definite valvular disease developed after the attack of erythema nodosum. In other words, 5 of 61 patients followed up had rheumatic heart disease, but 4 of these had rheumatic heart disease

30. Solomon, H. A.: Subacute Bacterial Endocarditis: Treatment with Sulfapyridine and Intravenous Injections of Typhoparatyphoid Vaccine, New York State J. Med. 41:45, 1941.

showed any abnormality of the joints and the adjacent bones were entirely normal except for occasional atrophy from disuse.

Roentgenograms of the nasal accessory sinuses showed a high percentage of chronic sinusitis. In some patients this condition may have been a significant part of their disease, as could be discovered by the proper bacteriologic studies. Since sinusitis alone is common in New England, the roentgenologic findings are not significant.

Well defined Ghon tubercles were rare in the entire group, and only 1 patient had calcification in the hilar glands already present at the time of erythema nodosum. One patient had a diagnosis of bronchiectasis confirmed by bronchograms, made with the use of iodized oil U. S. P., some time before the onset of erythema nodosum.

PROGNOSIS AND TREATMENT

Severity of Illness.—In most patients the temperature was 99 to 101 F. (37.2 to 38.3 C.) during the acute phase of the illness. Higher temperatures were observed as follows: 102 to 103 F. (38.9 to 39.4 C.) in 30 patients, 103 to 104 F. (39.4 to 40.0 C.) in 15 patients, 104 to 105 F. (40.0 to 40.6 C.) in 3 patients and 105 F. (40.6 C.) in 1 patient. Headache, nausea, malaise and asthenia were most prominent in the patients with high fever. The course was often phasic, in one to three day cycles, corresponding to the appearance of new lesions or further manifestations in the joints. Accompanying respiratory infections were slow to clear up. Usually a steady improvement followed symptomatic treatment. Occasional patients remained acutely ill for months despite supportive therapy. Two patients were abruptly improved by tonsillectomy for obviously infected tonsils. A similar improvement has been previously observed.²⁹ It should be emphasized, therefore, that if erythema nodosum has not subsided in the usual two to five weeks and if the tonsils are the likely source of the inciting infection, they should be removed without delay. Prophylactic doses of penicillin can be used to limit provocative temporary exacerbations which may follow. Equally important is the removal of other obvious sources of infection. Unless these are eradicated, erythema nodosum may smolder on for an indefinite period.

Chemotherapy.—One patient seemed to improve immediately after treatment with sulfadiazine. Many other patients did not respond to sulfonamide chemotherapy, and several patients treated with intensive courses of penicillin—240,000 units a day—by uninterrupted intramuscular injections each two hours did not recover more rapidly than would be expected without specific therapy. Roentgen treatment of

29. Spink.^{1d} Pilot.^{8c}

Pohle³¹ have emphasized the tuberculous nature of the disease in their group of 20 patients on whom roentgenograms of the chest were made, 9 of whom had some degree of glandular enlargement. Rotnes⁴⁰ reported 110 of 181 patients (61 per cent) with pulmonary changes shown on roentgenologic examination. He classified the lesions as hilar adenitis (20 patients), hilar adenitis with parenchymatous changes (54 patients), parenchymatous changes only (22 patients) and other hilar changes (14 patients). Evidence from many sources suggests that erythema nodosum accompanying tuberculosis appears at the time the cutaneous reaction to tuberculin becomes positive, that is, during the primary complex. Although erythema nodosum may be produced with excessive amounts of tuberculin in previously sensitized persons, this pattern rarely occurs spontaneously. In these circumstances the pulmonary lesions accompanying erythema nodosum should follow the course of the primary complex. Unfortunately, Rotnes, Kerley, Paul and Pohle have not presented bacteriologic evidence of tuberculosis in their patients or evidence of follow-up examinations demonstrating subsequent fibrosis or calcification in the pulmonary fields. A limited number of follow-up examinations made on our patients has revealed a striking lack of subsequent evidence of tuberculosis.

If the pulmonary lesions of erythema nodosum are often not tuberculous, then how do they come about? In table 1 there are listed various forms of regional lymphadenopathy present during erythema nodosum. The commonest is cervical, presumably draining an infection of the throat. When the infection is at another site, as for instance on the scalp or arm, it is again the local lymph nodes which enlarge. It seems likely, therefore, that hilar adenitis is a similar regional adenopathy draining a pulmonary or bronchial infection or a profuse postnasal discharge.

We agree with Kerley²³ that roentgen treatment does not cause regression of the enlarged lymph nodes or hasten the course of the disease. In 1 of our patients a mild dose of roentgen rays to the mediastinum caused an unexpectedly severe general reaction. We would not advise roentgen treatment even as a diagnostic test. The same reaction has been noted after roentgen treatment of pulmonary and mediastinal sarcoidosis.

A final point is the relation of erythema nodosum to rheumatic fever. The evidence presented here suggests that erythema nodosum is not a form of rheumatic fever but occasionally may accompany or follow it. The history of similar disease in the family, common in

31. Paul, L. W., and Pohle, E. A.: Mediastinal and Pulmonary Changes in Erythema Nodosum, *Radiology* 37:131, 1941.

before the development of erythema nodosum. In 1 patient mentioned elsewhere fatal rheumatic carditis developed during erythema nodosum.

Follow-up roentgenologic examinations of the heart and lungs were made a year or more after the acute stage of the disease in 30 patients. None of these patients showed any roentgenographic evidence of pulmonary tuberculosis, and in none of them had calcification developed in the bronchial nodes. The follow-up period ranged from one to twenty-six years and averaged five years.

The enlargement of the lymph nodes persisted from three to twelve months, usually disappearing in five to seven months. The pulmonary changes were more evanescent, usually disappearing in a few weeks, but persisting in 1 patient for several months. In none of this group were coarse nodular or streaking areas subsequently found in the lungs, such as would be expected in sarcoidosis and as were reported by Kerley.²³

COMMENT

The multiplicity of unrelated infections and drugs known to initiate erythema nodosum has tended to obscure its common association with infections caused by beta hemolytic streptococci. In this series, not only was there a high incidence of respiratory infections antedating cutaneous lesions but also beta hemolytic streptococci were cultured in material from half of the patients who were studied bacteriologically. The occurrence of the disease with the physical evidence of other types of respiratory infections and during the season when these are prevalent suggests that a variety of common infectious agents are also the cause of erythema nodosum.

The low incidence of clinical tuberculosis is in contrast to the frequency of streptococcic infections associated with erythema nodosum. A limited number of tuberculin tests (29 out of 61 patients reacting positively) reflects only the incidence of positive reactors in the population at large in this region. In Rotnes' series a higher incidence was observed (94 per cent), but this may have another explanation. The pulmonary lesions which may accompany erythema nodosum have rarely been found to be due to tuberculosis in our series. Even individual patients with parenchymatous as well as hilar shadows in the roentgenograms of the chest have been found to be nontuberculous when carefully studied and followed up.

Our percentage of positive findings in roentgenograms of the chest is less than that in most series of cases, probably because we are including the milder forms of erythema nodosum. Kerley²³ has reported what we regard as a selected series of cases (28 out of 37 patients with positive signs in the roentgenograms), and, from his description, has included several patients with sarcoidosis. Paul and

4. Migratory polyarthrititis was a part of the clinical picture of erythema nodosum in 80 per cent of adults and in a third of the children. Isolated attacks of pains in the joints preceded and followed erythema nodosum. Ten per cent of the patients had a chronic form of the disease lasting from months to years.

5. Mild secondary anemia, cervical adenopathy and occasionally (13 per cent) enlarged hilar or bronchial nodes characterized the illness.

6. Erythema nodosum is thought to be a hypersensitivity disease. Individual predisposition, a variety of infectious and chemical agents and local trauma contribute to its occurrence. It is not a form of rheumatic fever.

cases of rheumatic fever,³² was unusual for our patients. The frequency (11 per cent) of preexisting rheumatic heart disease at the time of erythema nodosum, which has been noted before^{1d} and also in this study (4 per cent), is a reflection of the relation of the two diseases to streptococcic infections. Jones has pointed out that 65 per cent of young patients who have had rheumatic fever will show evidence of cardiac damage during a rheumatic attack and 86 per cent will have murmurs within eight years.³³ Although adults in whom rheumatic fever develops show a decreasing incidence of cardiac disease,³⁴ no such evidence as is reported by these observers followed erythema nodosum in this series. A follow-up for a longer term may reveal subsequent rheumatic heart disease, but studies on potential rheumatic heart disease at five and ten years³⁵ suggest that this is highly unlikely. It may be interesting to include erythema nodosum with rheumatic fever in the group of hypersensitivity diseases, but this is a generic rather than a direct relationship. The proper antigen in the properly sensitized and predisposed persons may produce erythema nodosum in 1 and rheumatic heart disease in another. The concurrence of the two diseases, however, is coincidental. For prognostic reasons, especially as regards life insurance, this distinction is important to make.

SUMMARY

1. The clinical features of erythema nodosum in 155 patients, 61 of whom were followed for one to twenty years, are presented.
2. The disease occurred oftener in women (86 per cent), appeared in patients at the ages of 3 to 66 years and usually developed during the winter months.
3. Associated respiratory infections accompanied 80 per cent of the attacks. In one half of the patients for whom cultures were done beta hemolytic streptococci were grown in material from the throat. Tuberculosis was an uncommon antecedent infection and rheumatic heart disease a rare sequela.

32. Wilson, M. G., and Schweitzer, M. D.: Familial Epidemiology of Rheumatic Fever: Genetic and Epidemiological Studies, *J. Pediat.* **22**:468 and 581, 1943. Wilson, M. G.: Hereditary Susceptibility in Rheumatic Fever: The Potential Rheumatic Family, *J. A. M. A.* **124**:1188 (April 22) 1944.

33. Jones, T. D., and Bland, E. F.: Clinical Significance of Chorea as a Manifestation of Rheumatic Fever: A Study in Prognosis, *J. A. M. A.* **105**:571 (Aug. 24) 1935.

34. Cohn, A. E., and Lingg, C.: The Natural History of Rheumatic Cardiac Disease: A Statistical Study, *J. A. M. A.* **121**:113 (Jan. 9) 1943.

35. Boone, J. A., and Levine, S. A.: The Prognosis in "Potential Rheumatic Heart Disease" and Rheumatic Mitral Insufficiency, *Am. J. M. Sc.* **195**:764, 1938.

of age the mean systolic pressures were between 117.5 and 120.1 mm. In females in the same age groups the mean systolic pressures were between 107.4 and 119 mm.

TABLE 1.—*Systolic Blood Pressure of Men by Age Groups, 1930-1942*

Age, Years	Number of Cases	Mode	Mean Pressure	Standard Error	Range
16.....	114	122.58	118.5	± 1.1214	90 to 149
17.....	1,694	121.87	121.1	± 0.3211	80 to 149
18.....	8,344	121.99	121.7	± 0.1418	60 to 209
19.....	6,470	122.68	122.3	± 0.1616	60 to 229
20.....	5,038	123.06	122.8	± 0.1769	70 to 199
21.....	4,615	122.90	122.5	± 0.1863	70 to 199
22.....	4,105	123.11	122.4	± 0.1847	70 to 209
23.....	3,554	123.42	122.3	± 0.1952	60 to 209
24.....	2,792	123.08	121.9	± 0.2161	80 to 189
25.....	1,934	122.54	121.6	± 0.2596	80 to 179
26.....	1,291	122.46	121.2	± 0.3072	80 to 179
27.....	916	123.50	121.7	± 0.3758	80 to 179
28.....	638	122.78	120.9	± 0.4362	90 to 189
29.....	463	122.25	120.5	± 0.5451	80 to 179
30.....	364	122.10	120.3	± 0.5960	90 to 169
31 to 35.....	853	122.10	120.7	± 0.4019	80 to 169
36 to 40.....	284	116.97	120.1	± 0.8028	90 to 209
41 and over.....	281	119.79	122.8	± 0.8603	80 to 189
Total.....	43,800	122.74	122.0	± 0.0592	60 to 229

TABLE 2.—*Systolic Blood Pressure of Women by Age Groups, 1930-1942*

Age, Years	Number of Cases	Mode	Mean Pressure	Standard Error	Range
16.....	159	107.35	109.2	± 1.0094	70 to 149
17.....	2,182	108.14	108.8	± 0.2600	70 to 159
18.....	7,432	106.94	108.3	± 0.1442	60 to 179
19.....	4,753	108.66	109.9	± 0.1789	60 to 179
20.....	4,273	110.85	111.0	± 0.1833	60 to 219
21.....	3,604	112.97	112.4	± 0.1844	70 to 179
22.....	2,786	113.28	112.9	± 0.2064	70 to 169
23.....	1,555	112.34	112.7	± 0.2807	70 to 189
24.....	956	112.98	113.0	± 0.3699	80 to 169
25.....	633	112.67	113.0	± 0.4403	70 to 159
26.....	427	112.95	112.3	± 0.5561	60 to 159
27.....	306	113.82	113.6	± 0.6288	80 to 149
28.....	299	113.00	113.9	± 0.6387	80 to 159
29.....	237	113.54	113.6	± 0.8866	90 to 149
30.....	226	114.57	115.1	± 0.8027	90 to 159
31 to 35.....	820	114.12	115.5	± 0.4586	70 to 189
36 to 40.....	442	115.90	116.7	± 0.6007	90 to 179
41 and over.....	368	122.67	125.3	± 0.9917	90 to 239
Total.....	31,458	110.61	111.0	± 0.0693	60 to 239

The material for the present study was obtained from the records of physical examinations made at the Students' Health Service at the University of Minnesota from 1930 through 1942. During this twelve year period, 75,258 persons were examined, of whom 43,800 were men and 31,458 were women. With the exception of a few faculty members, the group comprised university students. The blood pressure readings were

BLOOD PRESSURE READINGS OF 75,258 UNIVERSITY STUDENTS

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MINNEAPOLIS

MANY studies of blood pressure have been made on large numbers of persons of different ages representing supposedly normal, healthy people. From such studies certain ranges of blood pressure have been accepted as "normal" for various age groups, these "normal" ranges being in fact the averages of the groups. The examination of large samples of the population can add to the knowledge of what may be considered "normal," or at least most common, for the particular group examined. It is not our purpose to attempt to define the "normal" blood pressure for any age group, but to present data on blood pressure determinations on a large number of persons, most of whom are young adults.

In reviewing the literature, there is found rather wide variation in the average blood pressure levels in supposedly normal persons. Alvarez¹ found the systolic pressure in male university students to average 128.9 mm. of mercury, while the mean for the women was 117.3 mm. Diehl² reported blood pressure readings of male students at the University of Minnesota in the years 1922, 1923 and 1924. He found the mean systolic pressure to be 126.9 mm. in the year 1922. In 1923 and 1924 the mean systolic pressure was 122.7 mm. This difference was thought to be due to the fact that students having a systolic pressure of 140 mm. or more in the 1923 and 1924 groups were rechecked later in the examination; thus the effect of excitement on the blood pressure level was reduced, since the second reading was the one recorded. Robinson and Brucer³ studied a group of supposedly healthy persons reporting for periodic examinations. In males between 15 and 45 years

From the Students' Health Service, University of Minnesota.

1. Alvarez, W. C.: Blood Pressures in Fifteen Thousand University Freshmen, *Arch. Int. Med.* **32**:17 (July) 1923.

2. Diehl, H. S., and Sutherland, K. H.: Systolic Blood Pressures in Young Men, *Arch. Int. Med.* **36**:151 (Aug.) 1925.

3. Robinson, S. C., and Brucer, M.: Range of Normal Blood Pressure, *Arch. Int. Med.* **64**:409 (Sept.) 1939.

age is not seen in the mean systolic pressures of men (fig. 1). The range in systolic pressure in men was 60 to 229 mm., and in women, 60 to 239 mm.

TABLE 3.—*Diastolic Blood Pressure of Men by Age Groups, 1930-1942*

Age, Years	Number of Cases	Mode	Mean Pressure	Standard Error	Range
16.....	114	72.22	72.2	± 0.9305	40 to 109
17.....	1,694	72.65	72.3	± 0.2534	20 to 119
18.....	8,344	72.64	72.1	± 0.1136	0 to 129
19.....	6,470	73.14	72.9	± 0.1304	0 to 119
20.....	5,088	73.14	73.8	± 0.1382	0 to 119
21.....	4,615	74.30	74.8	± 0.1411	20 to 129
22.....	4,105	74.72	75.7	± 0.1414	30 to 129
23.....	3,554	78.17	76.2	± 0.1493	0 to 119
24.....	2,792	80.28	76.3	± 0.1646	40 to 119
25.....	1,934	80.24	76.9	± 0.2000	30 to 129
26.....	1,291	78.18	77.0	± 0.2293	50 to 119
27.....	916	79.39	77.6	± 0.2972	40 to 129
28.....	638	74.68	77.2	± 0.3396	50 to 119
29.....	463	80.84	77.7	± 0.4189	50 to 109
30.....	364	80.59	78.1	± 0.4343	50 to 119
31 to 35.....	853	81.00	77.9	± 0.3941	30 to 109
36 to 40.....	284	78.12	78.1	± 0.6890	50 to 119
41 and over.....	281	80.90	81.4	± 0.8725	50 to 119
Total.....	43,800	74.00	74.5	0 to 129

TABLE 4.—*Diastolic Blood Pressure of Women by Age Groups, 1930-1942*

Age, Years	Number of Cases	Mode	Mean Pressure	Standard Error	Range
16.....	159	71.43	67.3	± 0.8516	20 to 99
17.....	2,182	70.80	66.9	± 0.2149	20 to 109
18.....	7,432	70.62	66.6	± 0.1217	10 to 109
19.....	4,753	71.25	68.1	± 0.1463	10 to 129
20.....	4,273	71.66	69.7	± 0.1497	10 to 139
21.....	3,604	72.34	71.6	± 0.1493	10 to 119
22.....	2,786	72.44	72.1	± 0.1649	30 to 109
23.....	1,555	72.60	72.0	± 0.2300	20 to 109
24.....	956	72.65	72.5	± 0.2759	40 to 109
25.....	633	72.83	72.7	± 0.3489	40 to 109
26.....	427	71.80	71.5	± 0.4117	40 to 109
27.....	306	74.20	72.8	± 0.5530	40 to 109
28.....	299	73.57	72.9	± 0.5369	40 to 99
29.....	237	72.88	72.5	± 0.5813	40 to 99
30.....	226	73.12	73.7	± 0.5902	50 to 109
31 to 35.....	820	73.01	74.5	± 0.3292	30 to 109
36 to 40.....	442	77.00	76.2	± 0.4367	50 to 109
41 and over.....	368	81.56	79.4	± 0.6612	10 to 139
Total.....	31,458	71.78	69.7	10 to 139

The mean diastolic pressure in men of all ages was 74.5 mm., and in women, 69.7 mm. At each age the mean diastolic pressure was higher in men than in women. In both men and women there was a tendency for the mean diastolic pressure to increase with age. The range of diastolic blood pressure was from 0 to 129 mm. in men and from 10 to 139 mm. in women (tables 3 and 4).

made with a mercury manometer by the auscultatory method, with the student in a sitting position. In general, the diastolic reading was taken at the point at which the tone changed, although we cannot be certain that all examiners throughout the twelve year period conformed to this method.

The mean age for the men was 21.51 years, with a range from 16 to 70 years. The majority were between 17 and 26 years of age. For the women the mean age was 21.06 years, with a range from 16 to 66 years, and the majority were between 17 and 23.

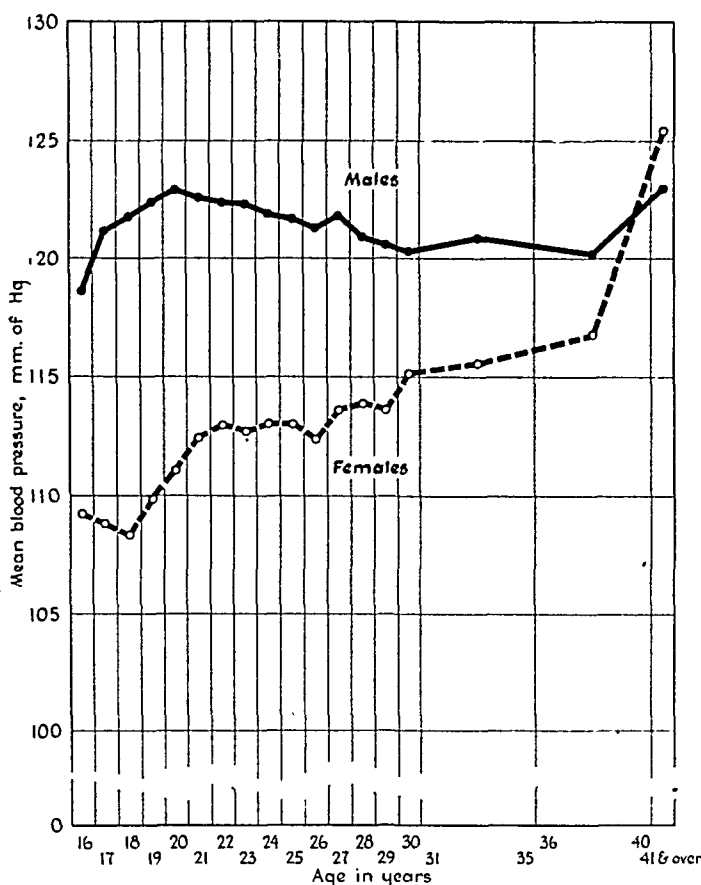


Fig. 1.—Mean systolic blood pressure by age and by sex.

The means and ranges of systolic blood pressure for each age group of men are presented in table 1. The same data for women are given in table 2. The mean systolic blood pressure for men of all ages included in this study was 122 mm., and for women, 111 mm. In every age group except the group over the age of 40 the mean systolic pressure in men exceeded that in women. The sex differences in mean systolic blood pressure are statistically significant in each age group except the group 41 years and over. In women there is a definite upward trend of the mean systolic blood pressure with age. This tendency to increase with

women. In the blood pressure range of 100 to 109 mm. were found 11.69 per cent of the men and 30.22 per cent of the women. This tendency for a greater percentage of women than men to have pressures below 109 mm. is seen at each age. The difference is statistically significant for each age group except the group 41 years and over.

Systolic pressures above 120 mm. occurred more frequently in men than in women. In the levels above 130 mm. the percentage frequency was greater in men than in women for each age group except the group

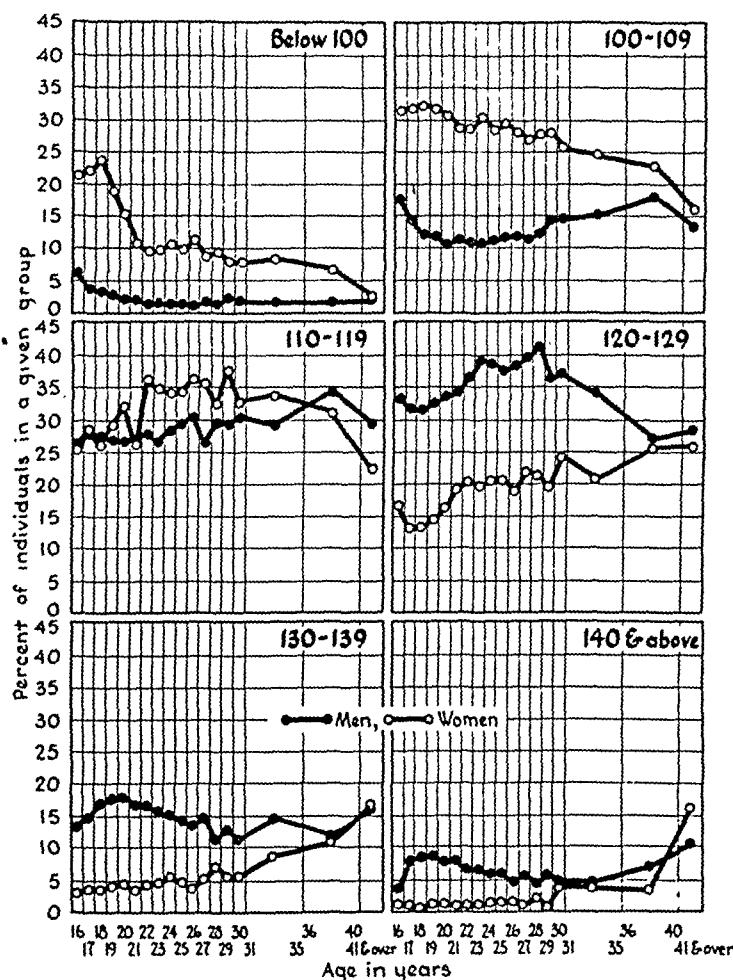


Fig. 2.—Percentage of men and of women in various systolic blood pressure groups.

41 years and over, with the differences statistically significant except in the group aged 16 and the groups 30 years of age and over.

Of the men, 63.39 per cent had systolic readings between 110 and 129 mm. Of the women, however, only 47.84 per cent had systolic pressures between 110 and 129 mm. The majority of the women (61.39 per cent) had systolic pressures between 100 and 119 mm. These age and sex differences are shown graphically in figure 2.

There seems to be little relation between age and systolic pressure levels in men, as shown by the percentage frequency of each age in the

In order to obtain further information on the effect of age on blood pressure levels, the blood pressure readings were divided into six groups

TABLE 5.—Percentage Frequency of Systolic Blood Pressure Levels of Men by Age

Age, Years	Below 100		100 to 109		110 to 119		120 to 129		130 to 139		140 and Above	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
16.....	7	6.14	20	17.54	30	26.32	38	33.33	15	13.16	4	3.51
17.....	64	3.78	238	14.05	472	27.86	538	31.76	251	14.82	131	7.73
18.....	283	3.39	1,033	12.38	2,323	27.84	2,628	31.50	1,403	16.81	674	8.08
19.....	178	2.75	766	11.84	1,747	27.00	2,100	32.46	1,135	17.54	544	8.41
20.....	120	2.36	534	10.50	1,368	26.89	1,729	33.98	911	17.90	426	8.37
21.....	103	2.23	520	11.27	1,256	27.22	1,583	34.30	783	16.97	370	8.02
22.....	65	1.58	437	10.65	1,136	27.67	1,509	36.76	682	16.61	276	6.72
23.....	57	1.60	373	10.50	955	26.87	1,386	39.00	555	15.62	228	6.42
24.....	43	1.54	309	11.07	783	28.04	1,073	38.43	423	15.15	161	5.77
25.....	28	1.45	220	11.38	572	29.58	726	37.54	275	14.22	113	5.84
26.....	16	1.24	153	11.85	390	30.21	495	38.34	173	13.40	64	4.96
27.....	18	1.97	104	11.35	242	26.42	365	39.85	137	14.96	50	5.46
28.....	8	1.25	79	12.38	189	29.62	262	41.07	72	11.29	28	4.39
29.....	10	2.16	66	14.26	136	29.37	168	36.28	58	12.53	25	5.40
30.....	7	1.92	53	14.56	110	30.22	135	37.09	41	11.26	18	4.94
31 to 35.....	15	1.76	128	15.01	249	29.19	294	34.47	125	14.65	42	4.92
36 to 40.....	5	1.76	51	17.96	97	34.15	77	27.11	34	11.97	20	7.04
41 and over.	5	1.78	37	13.17	83	29.54	82	29.18	45	16.01	29	10.32
All ages.....	1,032	2.36	5,121	11.69	12,138	27.71	15,188	34.68	7,118	16.25	3,203	7.31

TABLE 6.—Percentage Frequency of Systolic Blood Pressure Levels of Women by Age

Age, Years	Below 100		100 to 109		110 to 119		120 to 129		130 to 139		140 and Above	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
16.....	34	21.38	50	31.45	41	25.79	27	16.98	5	3.14	2	1.26
17.....	484	22.18	692	31.71	624	28.60	281	12.88	79	3.62	22	1.01
18.....	1,756	23.63	2,406	32.37	1,960	26.37	970	13.05	269	3.62	71	0.96
19.....	900	18.94	1,509	31.75	1,389	29.22	687	14.45	207	4.36	61	1.23
20.....	644	15.07	1,312	30.70	1,375	32.18	698	16.34	194	4.54	50	1.17
21.....	386	10.71	1,044	28.97	1,300	26.07	695	19.28	140	3.88	39	1.03
22.....	262	9.40	794	28.50	1,011	36.29	567	20.35	123	4.41	29	1.04
23.....	152	9.78	468	30.10	540	34.73	305	19.61	72	4.63	18	1.16
24.....	100	10.46	271	28.35	327	34.20	195	20.40	51	5.33	12	1.26
25.....	60	9.48	186	29.38	218	34.44	130	20.54	31	4.90	8	1.26
26.....	48	11.24	123	28.81	154	36.06	80	18.74	16	3.75	6	1.41
27.....	27	8.82	83	27.12	109	35.62	67	21.90	16	5.23	4	1.31
28.....	28	9.36	83	27.76	98	32.78	63	21.07	21	7.02	6	2.01
29.....	19	8.02	66	27.85	89	37.55	47	19.83	13	5.49	3	1.27
30.....	18	7.96	58	25.66	74	32.74	55	24.34	13	5.75	8	3.54
31 to 35.....	68	8.29	202	24.63	275	33.54	171	20.85	72	8.78	32	3.90
36 to 40.....	30	6.79	101	22.85	137	31.00	112	25.34	47	10.63	15	3.39
41 and over.	10	2.72	59	16.03	83	22.55	95	25.82	62	16.85	59	16.03
All ages.....	5,027	15.98	9,506	30.22	9,804	31.17	5,245	16.67	1,431	4.55	445	1.41

ranging from low to high. The percentage of persons of each age falling into these six groups was computed (tables 5 and 6). For all ages included in the study, 2.36 per cent of the men had a systolic blood pressure below 100 mm., compared with 15.98 per cent of the

both men and women. As in the systolic blood pressure, the notable exception to this trend to increase with age is in the age group 41 years and over.

TABLE 7.—Percentage Frequency of Diastolic Blood Pressure Levels of Men by Age

Age, Years	0 to 49		50 to 59		60 to 69		70 to 79		80 to 89		90 and Above	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
16.....	2	1.75	10	8.77	31	27.19	43	37.72	25	21.93	3	2.63
17.....	37	2.18	149	8.80	454	26.80	614	36.25	360	21.25	80	4.72
18.....	180	2.16	773	9.26	2,248	26.94	3,044	56.48	1,719	20.60	380	4.55
19.....	128	1.98	520	8.04	1,605	24.81	2,421	37.42	1,467	22.67	329	5.09
20.....	63	1.24	334	6.56	1,222	24.02	1,940	38.13	1,261	24.78	268	5.27
21.....	44	0.95	236	5.11	978	21.19	1,876	40.65	1,191	25.81	290	6.28
22.....	24	0.58	161	3.92	768	18.71	1,722	41.95	1,164	28.36	266	6.48
23.....	17	0.48	112	3.15	621	17.47	1,513	42.57	1,056	29.71	235	6.61
24.....	9	0.32	86	3.08	508	18.20	1,147	41.08	856	30.66	186	6.66
25.....	6	0.31	46	2.38	321	16.60	812	41.99	599	30.97	150	7.76
26.....	0	0	24	1.86	209	16.19	565	43.76	397	30.75	96	7.44
27.....	3	0.33	19	2.07	129	14.08	388	42.36	297	32.42	80	8.73
28.....	0	0	13	2.04	104	16.30	272	42.63	191	29.94	58	9.09
29.....	0	0	10	2.16	73	15.77	185	39.96	149	32.18	46	9.94
30.....	0	0	5	1.37	49	13.46	151	41.48	127	34.89	32	8.79
31 to 35.....	2	0.23	15	1.76	124	14.54	335	39.27	296	34.70	81	9.50
36 to 40.....	0	0	3	1.06	39	13.73	125	44.01	89	31.34	28	9.86
41 and over.	0	0	2	0.71	24	8.54	102	36.30	102	36.30	51	18.15
All ages.....	515	1.18	2,518	5.75	9,507	21.70	17,255	39.39	11,346	25.90	2,659	6.07

TABLE 8.—Percentage Frequency of Diastolic Blood Pressure Levels of Women by Age

Age, Years	0 to 49		50 to 59		60 to 69		70 to 79		80 to 89		90 and Above	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
16.....	8	5.03	30	18.87	51	32.08	49	30.82	18	11.32	3	1.89
17.....	92	4.21	414	18.97	775	35.52	659	30.20	208	9.53	34	1.56
18.....	392	5.29	1,453	19.55	2,602	35.01	2,127	28.62	728	9.80	129	1.73
19.....	187	3.93	750	15.78	1,610	33.87	1,568	32.99	547	11.51	91	1.91
20.....	121	2.83	508	11.89	1,367	31.99	1,595	37.33	588	13.76	94	2.20
21.....	44	1.22	293	8.13	1,052	29.19	1,497	41.54	636	17.65	82	2.28
22.....	27	0.97	206	7.39	794	28.50	1,186	42.57	494	17.73	79	2.84
23.....	20	1.29	121	7.78	434	27.91	648	41.67	288	18.52	44	2.83
24.....	6	0.63	63	6.59	268	28.03	409	42.78	182	19.04	28	2.93
25.....	5	0.79	39	6.16	173	27.33	272	42.97	124	19.59	20	3.16
26.....	6	1.40	28	6.56	132	30.91	187	43.79	65	15.22	9	2.11
27.....	3	0.98	25	8.17	79	25.82	120	39.22	66	21.57	13	4.25
28.....	3	1.00	26	8.70	69	23.08	126	42.14	62	20.74	13	4.35
29.....	4	1.69	15	6.33	61	25.74	106	44.73	45	18.99	6	2.53
30.....	1	0.44	13	5.75	57	25.22	93	41.15	52	23.01	10	4.43
31 to 35.....	4	0.49	46	5.61	184	22.44	329	40.12	208	25.37	49	5.97
36 to 40.....	1	0.23	14	3.17	88	19.91	178	40.27	126	28.51	35	7.92
41 and over.	1	0.27	12	3.26	59	16.03	117	31.79	119	32.34	60	16.31
All ages.....	926	2.94	4,056	12.89	9,855	31.33	11,266	35.81	4,556	14.48	799	2.54

The sex differences in diastolic pressures followed the same pattern as in the systolic pressures, a much larger percentage of women than men having levels below 70 mm.

various pressure groups (table 5). It must be kept in mind, however, that over 98 per cent of the men in this study were under 26 years of age. In the women in this study, age and blood pressure seem to be somewhat related, since there was a definitely greater percentage of younger women with pressures below 100 mm. Although the difference is not as striking, there was a tendency for more women in the older age groups than in the younger groups to have pressures above 120 mm. While some of these age differences are statistically significant, the

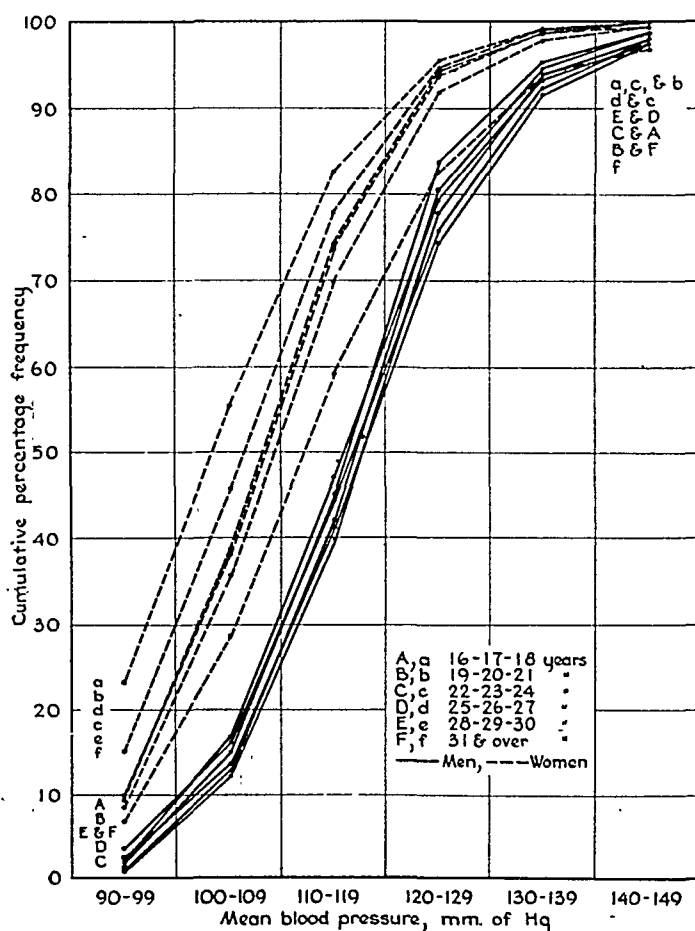


Fig. 3.—Cumulative percentage frequencies of mean systolic blood pressure by age groups and by sex.

trend is not constant. Figure 3 shows the cumulative percentage frequencies of systolic blood pressure levels by age groups and sex which illustrate these age and sex differences.

The tendency for the diastolic blood pressure to increase with age in both men and women, as indicated in tables 3 and 4, is again shown when the percentage frequency of diastolic pressure levels by ages is calculated (tables 7 and 8). With a few exceptions, the differences in diastolic pressure in various age groups are statistically significant in

INCIDENCE AND CLINICAL SIGNIFICANCE OF CORONARY ARTERY DISEASE IN DIABETES MELLITUS

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THE INCIDENCE of coronary artery disease in diabetic persons has been investigated repeatedly at autopsy, with general agreement that severe coronary arteriosclerosis is more frequent in the diabetic than in the nondiabetic patient.¹ Of 316 patients with diabetes over the age of 40 included in the report of Root, Bland, Gordon and White,^{1a} 38.2 per cent of the men and 32.2 per cent of the women had coronary

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SUMMARY

The results of blood pressure determinations on 75,258 persons examined at the Students' Health Service are presented. There were 43,800 men and 31,458 women in the group, most of whom were under 26 years of age.

The mean systolic blood pressure for men of all ages was 122 mm., and for women, 111 mm.

The mean systolic blood pressure of women showed a tendency to rise with age. This trend was not seen in men.

The mean diastolic pressure of men was 74.5 mm. and of women, 69.7 mm.

In both men and women there was a tendency for the diastolic pressure to increase with age.

A greater percentage of women than men had systolic pressures below 109 mm., whereas systolic pressures above 120 mm. occurred more frequently in men except in the age group 41 years and over. Approximately two thirds of the men had systolic pressures between 110 and 129 mm., while about two thirds of the women had systolic pressures between 100 and 119 mm.

The sex differences in diastolic pressures followed the same pattern as in the systolic pressures.

scarring of the ventricular muscle in regions other than the annulus fibrosus of the valves, the tips of the papillary muscles or the immediate vicinity of the blood vessels.

Such myocardial fibrosis was found in all 28 diabetic hearts with old coronary artery occlusions and narrowings. In contrast (table 1), the 6 diabetic hearts without narrowed coronary arteries showed no such fibrosis. Nine of the 16 intermediate hearts with narrowed arteries without complete occlusions showed myocardial fibrosis. These 9 hearts were therefore considered to have 3 plus coronary arteriosclerosis. The remaining 7 hearts, with narrowed arteries but no fibrosis, were graded as presenting 2 plus coronary arteriosclerosis.

Intercoronary anastomoses have also been considered to be a compensatory sequel to the development of significant coronary artery narrowing, although such anastomoses also occur in a small percentage of normal hearts.² In this series, all 28 hearts with old arterial occlusions and narrowings and myocardial fibrosis exhibited intercoronary anastomoses

TABLE 1.—*Functional Significance of Coronary Arteriosclerosis*

Degree of Sclerosis	No. of Hearts	Arterial Narrowings	Old Arterial Occlusions	Myocardial Fibrosis	Anastomoses	Functional Significance
0 to 1+	6	0	0	0	0	} Not functionally significant (13)
2+	4	+	0	0	0	
	3	+	0	0	+	
3+	3	+	0	+	0	} Functionally significant (37)
	6	+	0	+	+	
4+	28	+	+	+	+	

as well. The 6 hearts without such occlusions, narrowings or fibrosis showed no anastomoses. In the intermediate group, anastomoses were slightly more frequent in the hearts showing fibrosis (3 plus coronary arteriosclerosis) than in those in which the myocardium was not thus affected (2 plus arteriosclerosis). As thus differentiated, 3 plus and 4 plus coronary arteriosclerosis was considered to have been functionally significant during life and 1 plus to 2 plus sclerosis to have been of lesser functional significance.

Degree of Coronary Arteriosclerosis in Hearts of Diabetic and Non-diabetic Patients.—The average age of the 50 diabetic patients was 64.7 years; none was less than 42 years old at the time of death. The non-diabetic control series of hearts was therefore restricted to those from 400 consecutive and contemporary patients over the age of 40. The average age of the control group was 61.1 years. As in other studies,^{1a, c} women predominated among the 50 diabetic patients, only 19 (38 per cent) of whom were men. Among the controls were 255 (64 per cent) men and 145 (36 per cent) women.

The degree of coronary arteriosclerosis in these two groups is indicated in table 2. Functionally significant coronary arteriosclerosis

artery occlusions. The same study demonstrated such occlusions in only 9.9 per cent of 1,521 nondiabetic men and in 4.9 per cent of 789 nondiabetic women, all over the age of 40. In the same age group Enklewitz^{1b} found coronary artery occlusions in 31.8 per cent of 261 persons with diabetes.

In the hearts of a group of unselected patients studied by an improved technic of injection plus dissection for the detection of pathologic alterations in the coronary arteries,² one of us has found that arterial occlusions were almost as frequent as in previously reported series of diabetic hearts studied by routine methods.³ Included in a consecutive series of 643 hearts studied by this improved technic were 54 (8.4 per cent) from patients with a clinical diagnosis of diabetes mellitus. Because their glycosuria was discovered only during the terminal illness, 4 of these patients were not considered to have proved diabetes. The diagnosis of diabetes mellitus in the remaining 50 patients was based on adequate history and laboratory evidence, and their hearts were made the basis of an analysis of the relationship of diabetes to coronary heart disease.

FUNCTIONALLY SIGNIFICANT CORONARY ARTERIOSCLEROSIS

The coronary artery tree of every one of the 50 diabetic hearts showed some arteriosclerosis. Six of the diabetic hearts showed so little that no note of coronary artery narrowing was made during the dissection of the injected vessels and no narrowing was detectible in the roentgenogram of the injected coronary artery tree. These 6 hearts were considered to show 0 to 1 plus coronary arteriosclerosis (table 1). At the other extreme were 28 diabetic hearts containing one or more points of arterial narrowing and one or more old complete arterial occlusions which antedated the terminal illness. These were considered to show 4 plus coronary arteriosclerosis.

The remaining 16 hearts showed an intermediate degree of coronary arteriosclerosis. Dissection showed definite narrowing of the lumen at one or more points of the coronary artery tree but no arterial occlusion. Rather than rely entirely on this purely subjective impression of the degree and extent of arterial narrowing, the collateral evidence of myocardial fibrosis and of intercoronary anastomosis was utilized to evaluate the functional significance of narrowing of the coronary arteries. The degree of myocardial fibrosis may be considered an objective anatomic measure of the functional significance of coronary arteriosclerosis in the absence of other etiologic factors. For the purposes of this evaluation, myocardial fibrosis was accepted as present only when there was definite

2. Schlesinger, M. J.: An Injection Plus Dissection Study of Coronary Artery Occlusions and Anastomoses, *Am. Heart J.* **15**:528-568 (May) 1938.

3. Schlesinger, M. J., and Zoll, P. M.: Incidence and Localization of Coronary Artery Occlusions, *Arch. Path.* **32**:178-188 (Aug.) 1941.

occlusive episode of coronary artery disease. Rabinowitch, Ritchie and McKee⁴ found only 19 patients (1.3 per cent) with this condition in a group of 1,500 patients with diabetes. Root and Graybiel⁵ encountered but 210 patients (3 per cent) with angina pectoris among 7,000 diabetic persons of all ages. On the other hand, Edeiken⁶ observed angina pectoris in 8 per cent and thoracic pain of uncertain origin in another 5 per cent of a group of 100 diabetic patients unselected as to age, while Friedman⁷ made the diagnosis of angina pectoris in 9 per cent of a large group of diabetic persons over the age of 40. The low incidence of angina pectoris reported by these observers in patients who are known to have a high incidence of severe coronary artery disease seems inconsistent.

For the purpose of this report, the clinical records of all 450 patients were reviewed, and the diagnosis of angina pectoris was accepted only on the basis of "a syndrome consisting of paroxysmal substernal or

TABLE 4.—Incidence of Angina Pectoris in Diabetic and Nondiabetic Patients

Degree of Sclerosis	1+ to 2+ Not Functionally Significant		3+ to 4+ Functionally Significant		Total	
	Angina	No Angina	Angina	No Angina	Angina	No Angina
Diabetic						
Male (19)	0	4	6	9	6	13
Female (31)	1	8	7	15	8	23
Total (50)	1	12	13	24	14	36
Nondiabetic						
Male (255)	4	133	46	72	50	205
Female (145)	3	111	6	25	9	136
Total (400)	7	244	52	97	59	341

precordial pain or discomfort of short duration, not infrequently radiating to the shoulders and inner aspect of the arms, precipitated by exertion, emotion or other states in which the work of the heart is increased and relieved by rest or nitroglycerin."⁸

Angina pectoris thus defined was diagnosed, with no significant sex difference (table 4), in 14 (28 per cent) of the 50 diabetic patients and

4. Rabinowitch, I. M.; Ritchie, W. L., and McKee, S. H.: A Statistical Evaluation of Different Methods for the Detection of Arteriosclerosis in Diabetes Mellitus, *Ann. Int. Med.* **7**:1478-1490 (June) 1934.

5. Root, H. F., and Graybiel, A. J.: Angina Pectoris and Diabetes Mellitus, *J. A. M. A.* **96**:925-928 (March 21) 1931.

6. Edeiken, J.: Diabetes Mellitus as Observed in One Hundred Cases for Ten or More Years: II. Cardiac Studies, *Am. J. M. Sc.* **209**:8-16 (Jan.) 1945.

7. Friedman, G.: Cardiovascular Status of Diabetic Patients After the Fourth Decade of Life, *Arch. Int. Med.* **55**:371-394 (March) 1935.

8. Blumgart, H. L.; Schlesinger, M. J., and Davis, D.: Studies on the Relation of the Clinical Manifestations of Angina Pectoris, Coronary Thrombosis and Myocardial Infarction to the Pathologic Findings, *Am. Heart J.* **19**:1-91 (Jan.) 1940.

occurred in 37 (74 per cent) of the 50 diabetic patients but in only 149 (37 per cent) of the 400 controls. The relative immunity of non-diabetic women to severe coronary artery disease was striking, although male and female diabetic patients were equally affected. Old coronary artery occlusions were present in 55 per cent of the diabetic women but in only 6 per cent of the nondiabetic women.

If fresh as well as old arterial occlusions are taken into consideration, the difference between hearts from diabetic patients and those from

TABLE 2.—*Degree of Coronary Arteriosclerosis in Diabetic and Nondiabetic Patients Over the Age of 40*

Degree of Sclerosis	50 Diabetic Patients						400 Nondiabetic Patients					
	Male		Female		Total		Male		Female		Total	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Not functionally significant												
1+	1	5	5	16	6	12	97	38	101	70	198	50
2+	3	16	4	13	7	14	40	16	13	9	53	13
Functionally significant												
3+	4	21	5	16	9	18	51	20	22	15	73	18
4+	11	58	17	55	28	56	67	26	9	6	76	19
Totals.....	19	100	31	100	50	100	255	100	145	100	400	100

TABLE 3.—*Incidence of Coronary Artery Occlusions in Hearts of Diabetic and Nondiabetic Patients*

Type of Occlusion	Diabetic Patients			Nondiabetic Patients		
	Men (19)	Women (31)	Total (50)	Men (255)	Women (145)	Total (400)
Old.....	7	11	18	48	6	54
Fresh.....	2	2	4	15	2	17
Fresh and old.....	4	6	10	15	3	18
Total.....	13 (68%)	19 (61%)	32 (64%)	78 (31%)	11 (8%)	89 (23%)

nondiabetic patients is even more marked (table 3). Old or fresh arterial occlusions were found in 32 (64 per cent) of the 50 diabetic hearts and as frequently in women as in men. In 18 of these 32 hearts the occlusions were old, in 4 they were fresh and in 10 they were both fresh and old. Similar occlusions, however, were found in only 23 per cent of the controls, occurring in 31 per cent of the nondiabetic men and in but 8 per cent of the nondiabetic women. Thus, diabetic persons are twice as likely to have coronary artery occlusions as are nondiabetic men and eight times as likely as are nondiabetic women.

Angina Pectoris.—Various observers have reported on the incidence of angina pectoris in diabetes. Wilder¹¹ considered angina pectoris uncommon in persons with diabetes except in association with an

functionally significant coronary arteriosclerosis showed fresh cardiac infarcts at autopsy (table 5). Only 9 of these hearts had fresh coronary thrombotic occlusions. Four exhibited old arterial occlusions only and 1 arterial narrowings only. In 8 instances, old occlusions accompanied the fresh thrombotic occlusions.

These 14 hearts did not represent the total mortality in the diabetic group directly due to acute coronary artery disease. In 3 additional patients with functionally significant coronary arteriosclerosis, the interval between the onset of clinical symptoms of acute coronary failure and the time of death was too short to permit the development of a recognizable infarct. In each of these 3 hearts multiple old arterial occlusions and narrowings were present, and in 1 of them there was also a fresh thrombotic occlusion.

TABLE 5.—*Death from Coronary Heart Disease in Patients with Functionally Significant Coronary Arteriosclerosis*

	Diabetic Patients (37)			Nondiabetic Patients (149)		
	Coronary Deaths (17)		Noncoronary Deaths (20)	Coronary Deaths (55)		Noncoronary Deaths (94)
	With Fresh Infarct	Without Fresh Infarct		With Fresh Infarct	Without Fresh Infarct	
Old occlusions.....	4	2	12	15	6	33
Fresh thrombotic occlusions.....	1	0	3	13	2	2
Fresh thrombotic and old occlusions.....	8	1	1	9	3	6
No occlusions.....	1	0	4	6	1	53
Total.....	14	3	20	43	12	94

The demonstration of a fresh thrombotic occlusion in a coronary artery tree does not of itself warrant the presumption that death was due to acute coronary failure. Such fresh thrombotic occlusions may occur terminally as a result of vascular collapse, with slowing of blood flow in the coronary arteries.¹² They do not necessarily cause symptoms or death. Four of the patients whose hearts showed fresh thrombotic occlusions without fresh infarction did not present the terminal clinical picture of acute coronary failure and their deaths were therefore not included as attributable to that condition.

In summary, 17 (34 per cent) of the entire group of 50 diabetic patients died with the clinical syndrome of acute coronary heart disease. In the control group of 400 nondiabetic patients, an identical analysis revealed the incidence of death from acute coronary heart disease to be only 14 per cent (table 5).

12. Blumgart, H. L.; Schlesinger, M. J., and Zoll, P. M.: Multiple Fresh Coronary Occlusions in Patients with Antecedent Shock, *Arch. Int. Med.* 68:181-198 (Aug.) 1941.

in 59 (15 per cent) of the 400 nondiabetic patients. Only 1 of the diabetic patients with angina pectoris did not have functionally significant coronary arteriosclerosis.⁹ One third of both the 37 diabetic and the 149 nondiabetic patients with functionally significant coronary arteriosclerosis had had angina pectoris. Consistent with their higher incidence of functionally significant coronary arteriosclerosis, both men and women with diabetes show a higher incidence of angina pectoris than do those without diabetes. The relative infrequency of angina pectoris in nondiabetic women over 40 years of age is striking.

The frequency with which angina pectoris was found in this series of patients is probably due to the special interest of our associates in coronary artery disease. Patients often do not volunteer symptoms which suggest the diagnosis of angina pectoris, particularly when the discomfort is mild. The frequency with which angina pectoris is discovered depends partly on the direct attempt of the physician to elicit a characteristic history.

Fresh Coronary Thrombotic Occlusion and Cardiac Infarction.—

Because of the high incidence of functionally significant coronary arteriosclerosis and of angina pectoris among diabetic patients, a parallel frequency of cardiac infarction might be expected. Warren,¹⁰ however, found only forty-one fresh infarcts and 10 instances of "coronary thrombosis without infarction" at autopsy on 440 diabetic patients of all age groups, an incidence of but 11.6 per cent. Beardwood¹⁰ reported that only 240 deaths (15 per cent) were attributable to coronary artery disease among the 1,579 patients with diabetes who died in Philadelphia during the years 1940 to 1942. However, Pollack, Dolger and Ellenberg¹¹ encountered "acute coronary thrombosis" in 20.4 per cent of 113 diabetic patients, unselected as to age, at autopsy. Among 87 patients with diabetes over the age of 40, Enklewitz¹⁰ demonstrated "coronary thrombosis" with or without infarction in 29.8 per cent, and a 30 per cent incidence of cardiac infarction in a series of 193 such patients was reported by Lisa, Magiday, Galloway and Hart.¹¹

In the present series, none of the 13 diabetic patients with hearts free from functionally significant coronary arteriosclerosis died with the clinical picture of acute cardiac infarction. Also, none of their hearts had a fresh coronary thrombotic occlusion or a cardiac infarct. However, 14 (38 per cent) of the 37 hearts from diabetic persons with

9. This was a 66 year old hypertensive woman with hemolytic anemia.

10. Beardwood, J. T.: Report of Diabetic Surveys in Philadelphia: Analysis of 1,579 Deaths in Diabetics in Philadelphia 1940-1942, Proc. New York Diabetes A. **11**:345-355 (Feb.) 1944.

11. Pollack, H.; Dolger, H. A., and Ellenberg, M.: An Analysis of the Diabetic Morbidity and Mortality in a General Hospital, Am. J. M. Sc. **202**:246-251 (Aug.) 1941.

insulin used (table 7). No definite correlation between the severity of the diabetes and the severity of coronary arteriosclerosis was found.

However, there was a direct relationship between the degree of such sclerosis and the duration of the diabetes (table 8). The known duration of the diabetes could be determined from the histories of 47 patients. The average duration of diabetes at the time of death in 36 patients with functionally significant coronary arteriosclerosis was almost twice the average duration of the disease in 11 patients whose coronary artery disease was not functionally significant. Since the average age of the two groups was approximately the same, this disproportion could not be explained on the basis of a difference in age.

Thus, the well established observation¹³ that the severity of coronary arteriosclerosis is more closely related to the duration than to the

TABLE 8.—*Relation of Duration of Diabetes to Severity of Coronary Arteriosclerosis*

	Coronary Arteriosclerosis Not Functionally Significant			Coronary Arteriosclerosis Functionally Significant		
	No. of Cases	Average Age, Yr.	Average Duration of Diabetes, Yr.	No. of Cases	Average Age, Yr.	Average Duration of Diabetes, Yr.
Male.....	3	67.0	5.3	14	64.3	11.2
Female.....	8	66.4	5.9	22	63.4	10.0
Total.....	11	66.6	5.7	36	63.9	10.5

severity of the diabetes is confirmed in this group of patients in which a high incidence of coronary artery disease was discovered.

COMMENT

Although advanced coronary artery disease is generally accepted as a frequent complication of diabetes, the high incidence of this complication has not been fully appreciated. In small part this has been due to the statistical inclusion of young persons with diabetes, in whom severe coronary artery disease, although not rare,¹³ is relatively infrequent. Of approximately 1,000,000 persons with diabetes in the United States, 25 per cent are estimated to be less than 44 years of age.¹⁴ The inclusion of these in any survey of coronary heart disease would tend to minimize the frequency with which this complication contributes to the morbidity and mortality of older diabetic patients.

A second factor is the survival of diabetic persons to ages at which coronary artery disease becomes more frequent and more severe even in persons without diabetes. Thus, the average age at death of persons

13. Root and others.^{1a} Root and Sharkey.^{1c} Rabinowitch and others.⁴ Root and Graybiel.⁵

14. Joslin, E. P.; Root, H. F.; White, P., and Marble, A.: *The Treatment of Diabetes Mellitus*, ed. 8, Philadelphia, Lea & Febiger, 1946.

RELATIONSHIP OF HYPERTENSION TO CORONARY ARTERY DISEASE
IN DIABETIC PATIENTS

Hypertension was found by Root and Sharkey^{1c} in 53.1 per cent of 175 patients with diabetes of all age groups; it was found by Enklewitz^{1b} in 44 per cent and by Friedman⁷ in 46 per cent of diabetic persons over the age of 40. In diabetic^{1c} as well as in nondiabetic patients hypertension is thought to intensify the effects of coronary artery disease. The high incidence (74 per cent) of hypertension in our 50 diabetic men and women may be related to the high incidence of significant coronary artery disease in this series.

The diagnosis of hypertension was made in the patients in this series on the basis of recorded blood pressure readings of more than 150 mm.

TABLE 6.—*Relation of Hypertension to Heart Disease in Diabetic Patients*

	Nonhypertensive Patients (13)	Hypertensive Patients (37)
Deaths from acute coronary disease.....	2 (15%)	15 (41%)
Congestive heart failure.....	5 (38%)	22 (60%)
Myocardial fibrosis.....	5 (38%)	24 (65%)
Fresh or old cardiac infarct.....	0	18 (49%)

TABLE 7.—*Relation of Severity of Diabetes to Degree of Coronary Arteriosclerosis*

Severity of Diabetes	Coronary Arteriosclerosis		Totals
	Not Functionally Significant	Functionally Significant	
Mild (no insulin).....	6	16	22
Moderate (1 to 20 units of insulin daily).....	3	10	13
Severe (more than 20 units of insulin per day).. Total.....	2 11	11 37	13 48

of mercury systolic and of 90 mm. of mercury or more diastolic. In the few instances in which the hospital record of the terminal illness constituted our only recorded data, previous blood pressure readings were obtained from the family physician or from other hospitals.

As indicated in table 6, not only do hypertensive diabetic patients die more frequently from acute coronary heart disease than do the nonhypertensive but also congestive heart failure develops in them more often. The hearts of the hypertensive group more frequently exhibited diffuse myocardial fibrosis or actual myocardial infarction.

RELATIONSHIP OF SEVERITY AND DURATION OF DIABETES
TO SEVERITY OF CORONARY ARTERIOSCLEROSIS

In 48 of the diabetic patients the data were sufficiently complete for estimation of the severity of the disease as judged by the amount of

Early detection of symptoms due to this complication in the patient with diabetes, however, should lead to the early institution of a regimen designed to avoid or postpone so far as possible the onset of the sequelae of coronary arteriosclerosis.

The proper use of insulin is important in this respect, since insulin hypoglycemia, by causing stimulation of the sympathetic nervous system and the discharge of epinephrine,¹⁵ greatly increases cardiac work.¹⁶ By this mechanism, hypoglycemia may precipitate angina pectoris or even myocardial infarction. "Knife-edge" control of the blood sugar level in diabetic patients is therefore undesirable in the presence of coronary artery disease, since neither the activity nor the diet of most patients can be controlled continuously and with exactitude. Rather than risk hypoglycemia, therefore, it seems wiser to regulate the middle-aged or elderly diabetic patient so as to maintain the fasting blood sugar level at not less than 120 mg. per hundred cubic centimeters. In the absence of diabetic symptoms, ketonuria and loss of weight, such a constant mild hyperglycemia is preferable to a more rigid type of control which sooner or later will be complicated by insulin hypoglycemia.

It is doubtful whether such a control of diabetes will accelerate the rate of progression of coronary arteriosclerosis, since the severity of the diabetes, at least as measured by insulin requirement, has little relation to the degree of coronary arteriosclerosis. Furthermore, no correlation can be shown to exist in uncomplicated diabetes between the level of the blood sugar and hyperlipemia, since even in instances of poorly regulated diabetes the blood lipids may be within the normal range.¹⁷

SUMMARY AND CONCLUSIONS

Functionally significant coronary artery disease was disclosed in approximately three fourths of the hearts of 50 diabetic patients by means of postmortem injection plus dissection technic. One third of these patients had died of acute coronary heart disease. One quarter of the entire group had had angina pectoris.

Among diabetic women over the age of 40 the incidence of significant coronary arteriosclerosis, of angina pectoris and of death due to coronary artery disease is as great as among diabetic men. This is in

15. Cannon, W. B.; McIver, M. A., and Bliss, S. W.: Studies on the Condition of Activity in Endocrine Glands: XIII. A Sympathetic and Adrenal Mechanism for Mobilizing Sugar in Hypoglycemia, *Am. J. Physiol.* **69**:46-66 (June) 1924.

16. Ernestene, A. C., and Altschule, M. D.: The Effect of Insulin Hypoglycemia on the Circulation, *J. Clin. Investigation* **10**:521-528 (Aug.) 1931.

17. Man, E. B., and Peters, J. P.: Serum Lipoids in Diabetes, *J. Clin. Investigation* **14**:579-594 (Sept.) 1935. Chaikoff, I. L.; Smyth, F. S., and Gibbs, G. E.: The Blood Lipoids of Diabetic Children, *ibid.* **15**:627-631 (Nov.) 1936.

with diabetes has gradually risen from 44.5 years in 1898 to 64.5 years in 1945.¹⁴

Perhaps the most important factor in the underestimation of the severity of coronary heart disease in diabetic patients is the imperfection of routine methods of postmortem examination of the arteries. Occlusions have been demonstrated twice as frequently in such patients by the injection plus dissection technic as by previously reported conventional methods of examining the larger coronary arteries.³ Moreover, the use of this improved method, combined with the microscopic examination of the myocardium, makes it possible to establish rational criteria for estimating the functional significance of the coronary artery disease in a given heart.

The present study, utilizing the improved technic, demonstrated that at the time of death functionally significant coronary artery disease was present in approximately three fourths of our diabetic patients. In one third of the entire group the cause of death was acute coronary heart disease, and one quarter of the patients had had angina pectoris during life.

This high morbidity cannot be explained by the predominance of a particular racial group in this series. When studied by routine pathologic technics in both institutions, the incidence of coronary occlusions in a predominantly non-Jewish population at the Massachusetts General Hospital was 11.0 per cent, as compared to a 10.5 per cent incidence in the predominantly Jewish population at the Beth Israel Hospital.⁸ However, it is possible that the high incidence of functionally significant coronary heart disease in this series of diabetic patients is related to the high incidence of hypertension in the group.

In middle-aged persons with diabetes the clinical diagnosis of functionally significant coronary artery disease can be made more frequently by maintaining a high index of suspicion, obtaining a careful history and performing proper clinical and laboratory studies. Any diabetic man or woman over the age of 40 can be assumed to have advanced coronary artery disease even in the absence of symptoms, particularly if hypertension is present, and more particularly if the diabetes is of more than ten years' duration. Pain in the chest in a middle-aged diabetic patient should be considered as angina pectoris due to coronary heart disease unless some other disease can be shown to be the definite and sole cause of the complaint. On the other hand, absence of complaints suggestive of angina pectoris does not militate against the application of this general rule, inasmuch as it has been shown that angina pectoris often does not occur until multiple coronary artery occlusions and narrowings have already developed.⁸

In the absence of precise knowledge concerning the cause of arteriosclerosis, prevention of coronary artery disease is not now possible.

MARFAN'S SYNDROME IN THE ADULT

Dissecting Aneurysm of the Aorta Associated with Arachnodactyly

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ARACHNODACTYLY (Marfan's syndrome) is a relatively rare familial symptom complex which is familiar to ophthalmologists, pediatricians and, to a lesser extent, orthopedic surgeons. It should be of interest to all physicians. We wish to summarize its important characteristics and emphasize the aortic lesions which may be associated with it.

REVIEW OF THE LITERATURE

Although entitled dolichostenomelie by Marfan,¹ Archard² in 1902 emphasized the most characteristic feature of the syndrome, calling it arachnodactyly (spider fingers). In 1926 Piper and Irving-Jones,³ the first American physicians to record the condition, noted the frequency with which it is associated with congenital malformations of the heart. Futcher and Southworth⁴ in 1938 pointed out rheumatic endocarditis and pulmonary disorders as common medical complications. In 1943 Baer, Taussig and Oppenheimer⁵ reported 2 cases in which aneurysmal

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1. Marfan, A. B.: Un cas de déformation congénitale des quatre membres, plus prononcée aux extrémités, caractérisée par l'allongement des os avec un certain degré d'amincissement, Bull. et mém. Soc. méd. d. hôp. de Paris **13**:220-226 (Feb. 28) 1896.

2. Achard, C.: Arachnodactylie, Bull. et mém. Soc. méd. d. hôp. de Paris **19**:834-840 (Oct. 10) 1902.

3. Piper, R. K., and Irving-Jones, E.: Arachnodactylia and Its Association with Congenital Heart Disease, Am. J. Dis. Child. **31**:832-839 (June) 1926.

4. Futcher, P. H., and Southworth, H.: Arachnodactyly and Its Medical Complications, Arch. Int. Med **61**:693-703 (May) 1938.

5. Baer, R. W.; Taussig, H. B., and Oppenheimer, E. H.: Congenital Aneurysmal Dilatation of the Aorta Associated with Arachnodactyly, Bull. Johns Hopkins Hosp. **72**:309-317 (June) 1943.

sharp distinction to the sex difference in these respects in the non-diabetic population.

Angina pectoris, deaths due to acute coronary disease and congestive heart failure all are more common when hypertension is present in diabetic patients than when the blood pressure is normal.

The severity of the coronary arteriosclerosis is correlated with the duration but not with the severity of the diabetes.

Early detection of the symptoms of coronary artery disease in persons with diabetes is necessary if the sequelae of coronary arteriosclerosis are to be postponed or avoided.

Mild hyperglycemia is preferable to a regimen which may result in insulin hypoglycemia and the attendant risk of precipitating myocardial infarction.

side to side. Myopia is the rule, and vision is seriously impaired. The pupils are small, and the response to atropine is feeble.

The presence of a cardiac abnormality, congenital or acquired, is most common in arachnodactyly, and it is of interest that there is usually a paucity of symptoms in the presence of definitive clinical signs. The signs necessarily vary with the particular disorder. Roentgenograms of the chest may reveal cardiac enlargement, but their interpretation is commonly difficult because of thoracic deformities.

Congenital malformations of the lungs are frequent and, combined with thoracic deformity, make pulmonary disease a dangerous complication. Pneumonia is a particularly common cause of death.

All these abnormalities may be present in a single case; however, as a rule one or more will be missing. The presence of the commonest characteristics is sufficient for the diagnosis.

Heredity.—Formes frustes, with stigmas of the disease, may be noted among the siblings of a person with typical arachnodactyly. Young⁹ has described a brother and sister with ectopia lentis and arachnodactyly. Weve¹⁰ has published reports of a father with dislocations of the lenses who had sixteen children. Five of these died; four were believed to have had arachnodactyly. Of the eleven living children, three (two boys and a girl) had the characteristic habitus. Weve's second family consisted of a father, two sons and a daughter. All had the typical manifestations of the syndrome, and their paternal grandfather was said to have been similarly afflicted.

Sex.—Rados⁸ reviewed 204 cases, involving 101 males and 103 females.

Race.—Almost all the patients about whom case reports have been written are white, but arachnodactyly has been reported in Negroes by Fitcher and Southworth,⁴ Rambar and Denenholz,¹¹ and Baer, Taussig and Oppenheimer.⁵

Étiologic Factors.—The syndrome is of unknown origin, but many theories have been proposed. Salle¹² considered arachnodactyly to be the result of pituitary dysfunction and related to giantism and acromegaly. Weve¹⁰ emphasized the part played by fetal disturbance in mesodermal structures, but other authors have pointed out that some of the typical ocular findings are primarily the result of abnormalities

9. Young, M. L.: Arachnodactyly, Arch. Dis. Childhood **4**:190-214 (Aug.) 1929.

10. Weve, H.: Ueber Arachnodaktylie, Arch. f. Augenh. **104**:1-46 (May) 1931.

11. Rambar, A. C., and Denenholz, E. J.: Arachnodactyly, J. Pediat. **15**:844-852 (Dec.) 1939.

12. Salle, V.: Ueber einem Fall von angeborener abnormer Grösse der Extremitäten, Jahrb. f. Kinderh. **75**:540-550, 1912.

dilatation of the aorta was found at autopsy. The same year Etter and Glover⁶ described a case in which death resulted from dissecting aneurysm of the aorta. Parker and Hare⁷ in 1945 demonstrated roentgenologic evidence of aneurysmal dilatation of the aorta in a patient with arachnodactyly. A comprehensive review of the literature was published by Rados⁸ in 1942.

The diagnosis of arachnodactyly can usually be established by inspection if the examiner is familiar with the condition. In the majority of the cases the skull is dolichocephalic. The supraorbital ridges are prominent. There is bossing of the frontal eminences, and the eyes are sunken. The auricles of the ears are large and protruding, and the jaw juts forward. The teeth are long, narrow and irregularly spaced. The palate is high, arched, narrow and frequently cleft. These features, coupled with the fact that the wearing of glasses is a necessity for the majority of patients with this disease, tend to endow them with a serious, prematurely aged appearance. The limbs are exceedingly long and slender. The span between the tips of the middle fingers with the arms extended often is greater than the length. The metacarpal bones and the phalanges, especially the terminal phalanges, are increased in length, giving the fingers a delicate, spider-like appearance. The metatarsal bones and the toes are also long and slender. This slenderness and delicacy of the limbs, hands and feet are enhanced by the meager amount of subcutaneous fat and the poorly developed, hypotonic musculature. These abnormalities tend to give the general impression of emaciation. Laxity of ligamentous structures permits hypermobility of joints and may be marked enough to allow subluxation. The laxity of ligaments and the inadequate muscular development are believed to be the primary cause of the frequent spinal and thoracic deformities which do not appear until a child with this syndrome begins to walk. The spinal deformities are kyphosis and scoliosis; the thoracic deformity is usually characterized by a funnel chest, but pigeon breast, with narrowness and flattening of the thoracic wall, may be seen. Contractures, spurring of the os calcis, pes planus, hammer toes, club foot and spina bifida occulta are other not uncommon deformities.

The ocular defect is characteristic. This consists in congenital bilateral dislocation of the lenses. The iris, being unsupported by the lens, shows tremulousness (iridodonesis) when the head is moved from

6. Etter, L. E., and Glover, L. P.: Arachnodactyly Complicated by Dislocated Lens and Death from Rupture of Dissecting Aneurysm of Aorta, *J. A. M. A.* **123**:88-89 (Sept. 11) 1943.

7. Parker, A. S., Jr., and Hare, H. F.: Arachnodactyly, *Radiology* **45**:220-226 (Sept.) 1945.

8. Rados, A.: Marfan's Syndrome (Arachnodactyly Coupled with Dislocation of Lens), *Arch. Ophth.* **27**:477-538 (March) 1942.

affecting ectodermal structures. Passow¹³ considered the condition to be closely related to status dysraphicus or to microform syringomyelia, which has some features similar to those of arachnodactyly.

Summary of Postmortem Examinations.—Although over 200 cases of arachnodactyly have been reported, descriptions of only twelve autopsies are found in the literature. Of these, ten are more or less complete descriptions. A study of these cases does not offer any solution as to the cause of the syndrome, but its association with cardiac disease is strongly emphasized. All the patients exhibited the typical symptom complex. Only the cardiovascular and important general anatomic findings are tabulated (table 1).

REPORT OF CASES

The following 2 cases are of special interest in that the patients in both died suddenly of dissecting aneurysm of the aorta.

CASE 1.—The patient, a 22 year old white university student, suddenly fell to the classroom floor and died on Jan. 15, 1935. He had been seen in the University of Chicago Clinics when he first entered the university in November 1933 and had had no complaints. He was described as an asthenic, 20 year old youth measuring 79 inches (200 cm.) in height and weighing 157 pounds (71 Kg.). The external occipital protuberance and the supraorbital ridges were prominent. The deeply set eyes showed bilateral iridodonesis and congenital subluxation of the lenses. The palate was high and arched. There was a sternal deformity of the pigeon breast type. The limbs, hands and feet were long and slender, and the gracile fingers and toes were remarkably long. Bilateral contractural deformities of the third, fourth and fifth toes were noted. The body musculature was poorly developed and hypotonic. All the joints were excessively mobile. The generalized lack of subcutaneous fat was distinct. The heart was of normal size. A loud systolic and a soft diastolic murmur were heard at the base, with greatest intensity in the aortic area. The pulse rate was 104, and the blood pressure was 130 systolic and 58 diastolic.

Past History.—The patient had been a normal full term infant at birth in September 1913. He had had bronchopneumonia at the age of 6. At the age of 9 an ophthalmologist had prescribed glasses after noting the presence of bilateral congenital subluxation of the lenses. A tonsillectomy had been performed the following year. There was no history of rheumatic fever or chorea.

His family physician later contributed more information. He had first seen the patient (aged 9) in 1922, having been consulted because of the child's nervousness. The aforementioned deformities and the presence of an apical systolic murmur were noted. He believed the child to be of a "pituitary type." In 1927 he observed twitchings in the muscles of the boy's forearms but no other significant changes. In 1934 the patient returned, complaining of headaches. He had grown 24 inches (61 cm.) in the intervening seven years. The possibility of a pituitary tumor was considered, and roentgenograms disclosed a definitely enlarged but

13. Passow, A.: Analogie und Koordination von Symptomen der Arachnodaktylie und des Status dysraphicus, Klin. Monatsbl. f. Augenh. 94:102-103 (Jan.) 1935.

Postmortem Findings in Twelve Cases of Arachnoidactyly

Author	Sex and Age at Death	Anatomic Findings (Not Related to Heart and Aorta)	Heart and Aorta
Bergstrand ¹⁰	Female 19 days (premature)	Monolobed left lung; bronchopneumonia; microscopic: questionable increase in eosinophil cells in pars anterior of the hypophysis	Normal heart
Salle ¹³	Male 2½ mo.	Enlargement of the sella turcica; slight enlargement of the pituitary; exostosis of the sella; abnormal elongation of the intestines; microscopic: increase in eosinophil cells in pars anterior of the hypophysis	Dilatation of the heart; hypertrophy of the heart; patent foramen ovale (gray-red nodulations were noted along the margins of the tricuspid and aortic valves)
Börger ¹⁸	Female 1 yr.	Vestigial middle lobe of the right lung; abnormal enlargement of the lingula of the left lung; bronchopneumonia; microscopic: increase in eosinophil cells in pars anterior and crease in eosinophil cells in pars posterior	Patent foramen ovale; heart of normal size and shape
Piper and Irving-Jones ³	Female 21 mo.	Monolobed left lung and vestigial middle lobe of the right lung; normal hypophysis	Hypertrophy of the heart; interauricular septal defect
Rambar and Denenholz ¹¹	Male 27½ mo.	Bronchopneumonia; absence of the dilator pupillae bilaterally; normal hypophysis	Normal heart
Apert, E.; Nourrisson (Jan.) 1938	Female 13 yr.	Atherosclerosis of the pulmonary artery; vestigial middle lobe of the right lung	Hypertrophy of the right ventricle; patent ductus botalli
Baer, Taussig and Oppenheimer ⁵	Female 14 yr.	None *	Hypertrophic heart (560 Gm.); patent foramen ovale; wrinkling and nodulation of mitral valve; Macallum patch; dilatation of aortic orifice; displacement of coronary ostia upward; aneurysmal dilatation of the ascending aorta; congenital malformation of the aortic media; no evidence of old rheumatic activity
Olcott, C. T.; Am. J. Dis. Child. 60: 660-668 (Sept.) 1940	Female 16 yr.	Bronchopneumonia; cysts in the thyroid and in the pars intermedia of the hypophysis; hypoplasia of the uterus and ovaries; microscopic: round cell infiltration of the gastric mucosa	Hypertrophic heart (520 Gm.); fenestration of the posterior cusp of the mitral valve and calcification and nodular thickening of the mitral valve ring; acute vegetative endocarditis
Etter and Glover ⁶	Male 21 yr.	None *	Incomplete report stated: "aortic valvular regurgitation with pronounced myocardial hypertrophy and massive hemopericardium; chronic dissecting aneurysm of the ascending aorta with fatal rupture into pericardium"
Baer, Taussig and Oppenheimer ⁵	Male 25 yr.	Passive congestion of the liver; normal hypophysis	Hypertrophic heart (840 Gm.); dilatation of the heart; patent foramen ovale; thickening of the endocardium beneath the aortic valve; dilatation of the aortic orifice; aneurysmal dilatation of the ascending aorta; displacement of the coronary ostia upward; congenital malformation of the aortic media; no evidence of old rheumatic activity
Weill ¹⁵	Female 27 yr.	Microscopic: increase in eosinophil cells in pars anterior of the hypophysis	Dilated hypertrophic heart (490 Gm.); marked dilatation of the aortic orifice; fusion and thickening of the left and posterior aortic valve cusps; dilatation of the intrapericardial portion of the aorta with snail-like ectasia of the sinuses of Valsalva; healed endocarditis
Weill ¹⁵	Male 47 yr.	Enlarged thymus; defect in falx cerebri; symphysis of the frontal lobes; normal hypophysis	Heart of normal size and shape; yellowish thickening of gelatinous consistency covered the "free face" of the mitral valve; healed endocarditis or mucous degeneration

* The postmortem record on these patients was incomplete.

at this point. The tear, 13 mm. long, was located 7 cm. above the junction of the right and posterior aortic valve cusps. It communicated with the pericardial cavity after dissecting downward for a distance of 3 cm.

The right pleural cavity was obliterated by dense fibrous adhesions. The lungs had red, wet sectioned surfaces. The liver was congested. The remaining organs were grossly normal.

Microscopic Examination: The most remarkable changes were found in the aortic media, and the lesions, although severest in the region of the aneurysmal dilatation, were found in all sections of the aorta (fig. 2). The changes consisted in rarefaction, fragmentation, and, in some areas, complete disappearance of the elastica associated with proliferation of muscle fibers. Instead of lying parallel to one another in the usual fashion, the fibers ran irregularly in all directions. Groups of muscle fibers surrounded spaces filled with a coagulum which stained blue with

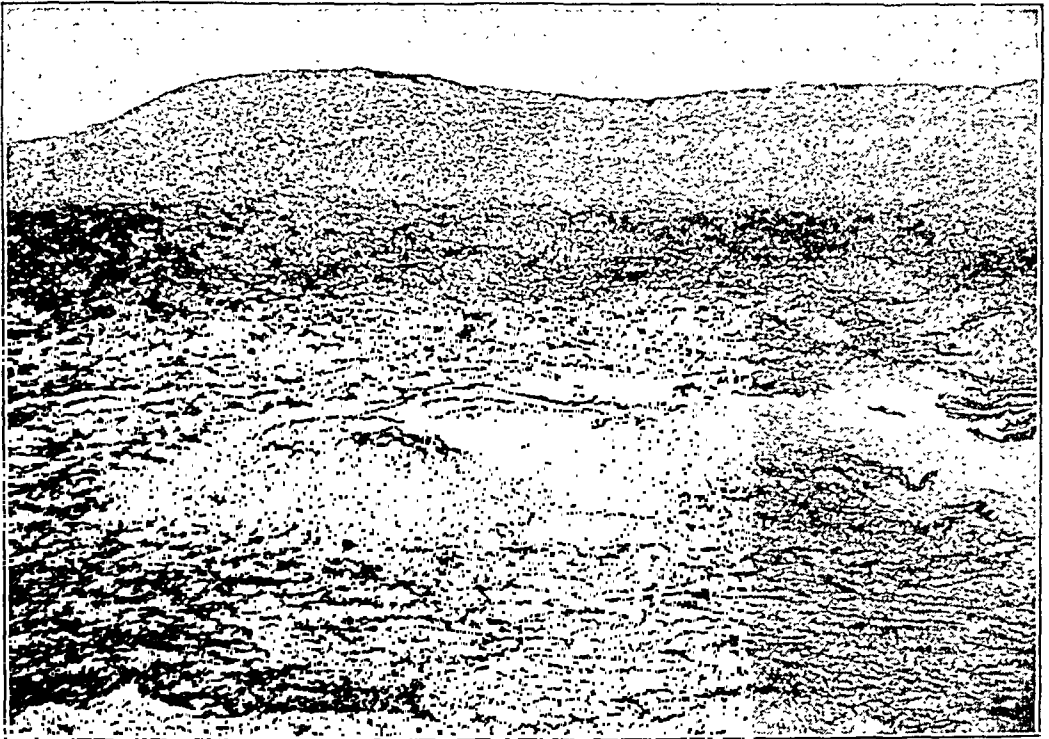


Fig. 2.—Aortic cystic medionecrosis (case 1). Muscle fibers are numerous in the aortic wall, and proliferation is conspicuous about the mucoid cysts and in spaces devoid of elastic lamellas. Phosphotungstic acid hematoxylin stain; $\times 55$.

hematoxylin and eosin. The spaces varied from cleftlike slits to large cystic cavities. The intima was thickened over the larger cavities, and the adventitia was widened, containing small lymphocytic foci. A sudan III stain demonstrated no fatty deposits. There was no evidence in any section of medial inflammation or recent necrosis.

The hypertrophic myocardium exhibited focal scarring and small areas of cellular infiltration closely related to the intermuscular collagenous septums. The infiltrating cells were lymphocytes and eosinophils, with rare neutrophilic leukocytes. The leaflets of the aortic and mitral valves were thickened by a myxomatous fibrous tissue. Neither the valvular nor the myocardial lesions were typically rheumatic.

The liver also contained small numbers of lymphocytes, plasma cells and eosinophils about portal triads and central veins. The gastric mucosa was moderately atrophic and showed mild gastritis. The lungs, liver and pancreas were

otherwise normal sella turcica. The blood pressure was 118 systolic and 62 diastolic. Loud systolic and soft diastolic basal murmurs were heard. An analgesic was prescribed for headache, and the patient was advised to limit his physical activity. The physician saw him for the last time in December 1934, one month prior to his death. He had been well and had no complaints. The blood pressure was 142 systolic and 80 diastolic. The pulse rate was 140 per minute. There were no other obvious changes in his physical condition.

Family History.—The patient's father and mother were living and well. Neither they nor their immediate relatives manifested any of the stigmas of arachnodactyly.

Autopsy.—The postmortem examination was performed twelve hours after death. The characteristic arachnodactylic abnormalities were as described in the clinical history. The main interest centered about the heart and aorta (fig. 1).

The pericardial sac was markedly distended and was found to be filled with 1,250 cc. of blood. There was a longitudinal tear in the intrapericardial portion of the ascending aorta. The pericardium, except for the area about the laceration,



Fig. 1.—Fusiform aortic aneurysm (case 1). The dilated sinuses of Valsalva are incorporated in the aneurysm, which terminates abruptly at the aortic arch. The tear lies high above the aortic valve. (Sections have been excised from its margin, and from the left cusp.)

was smooth and pale. The heart weighed 650 Gm. The right atrium and the tricuspid orifice were dilated. The right ventricle was small, and its muscular wall was firm and thick. The pulmonary orifice and the pulmonic trunk were normal. The ductus arteriosus and the foramen ovale were closed. The left atrium and the mitral orifice were normal. The muscle of the left ventricle was firm and hypertrophic. The aortic orifice measured 13 cm. The valve cusps were extremely large and thickened along the margins. The ostiums of the coronary arteries were located in an abnormally high position above the valve ring. The ascending aorta was dilated to approximately four times the normal size from the level of the valve ring upward for a distance of 14 cm. This dilatation formed a fusiform aneurysm measuring 19 cm. in its greatest circumference. The wall of the aneurysm was remarkably thin, striated and, in some areas, translucent. The dilatation ended abruptly 2 cm. below the innominate artery, and the aortic circumference was 5 cm.

with 86 per cent neutrophils; sedimentation rate, 5 mm. per hour, and hematocrit reading, 44 per cent. A urinalysis yielded normal results. An electrocardiogram on May 6 showed a tendency to right axis deviation but no evidence of myocardial infarction. Precordial pain persisted, requiring relatively large quantities of morphine during the next five days. A second electrocardiogram, on May 9, demonstrated that notable changes had occurred since May 6. The previously upright T waves had become inverted or diphasic in all leads, and the isoelectric S-T intervals had become depressed in leads II and III. These changes were interpreted as the result of digitalization or of pericarditis rather than as indicative of myocardial infarction. On the morning of May 10 the patient was found to be pale, cold, perspiring and complaining of severe pain in the lower thoracic and upper lumbar regions of the back. Her respirations were labored. The blood pressure and pulse rate were not obtainable in the right arm but were readily detectable in the left. The blood pressure was 136 systolic and 56 diastolic. These changes were accompanied with a precipitous rise in pulse rate to 140 per minute, a rise in



Fig. 3.—Dissecting aneurysm of the aorta (case 2). The primary laceration lies above the aortic valve, and the false passage has been laid open from the arch to the diaphragm.

temperature to 103.5 F. and an increase in respirations to 44 to 56 per minute. The following day the liver was palpable at the umbilicus, and the white blood cell count was recorded as 44,000. All these signs and symptoms persisted, the pain being of particular severity and requiring "demerol" (1-methyl-4-phenyl piperidine 4-carbonic acid), until death on May 14.

Clinical Diagnosis.—The clinical diagnosis was as follows: arachnodactyly, congenital heart disease with intraventricular septal defect and coronary occlusion with myocardial infarction.

Autopsy.—The postmortem examination was performed three and one-half hours after death. The arachnodactylic abnormalities were as described clinically. The heart and aorta were of greatest interest (fig. 3).

The pericardium was thin and translucent. In situ the entire right border of the heart was formed by the dilated right atrium. Because of the thoracic deformity the heart was twisted, and the pulmonary conus lay behind and to the left of the

congested. Sections of the anterior pituitary demonstrated poorly granulated basophilic cells and an apparent diffuse increase of small eosinophilic cells. The other endocrine glands, and the thymus were normal. The testes contained few maturing spermatozoa.

Anatomic Diagnosis.—The anatomic diagnosis was as follows: arachnodactyly; massive hemorrhage into the pericardial cavity secondary to rupture by dissection of a fusiform aneurysm of the ascending aorta; dilatation of the aortic orifice; malformation of the aortic media; cardiac hypertrophy; focal nonspecific myocarditis; scarring of the leaflets of the mitral and aortic valves; focal nonspecific hepatitis; subacute follicular and interstitial gastritis, and diffuse increase of eosinophilic cells in the hypophysis.

CASE 2.—The patient, a 35 year old white woman, was first seen in the University Eye Clinic in 1931 at the age of 19. Her parents became aware of her visual disturbances when she was 6 years old. Her right eye had been enucleated at the age of 7 because of panophthalmitis following needling of a cataract. The ocular findings recorded in 1931 were coloboma of the left lens and choroid with tremulousness of the left iris. The patient was described as a thin woman appearing older than the stated age. The external occipital protuberance and the frontal eminences were prominent. The right orbital cavity contained an artificial eye. The palate was high and arched. There was severe thoracic deformity characterized by funnel chest and kyphoscoliosis of the dorsal spine. Other characteristic and noteworthy general findings were spider-like fingers and toes, long slender limbs, poorly developed hypotonic musculature, hypermobile joints and generalized lack of subcutaneous fat. There was no history of arachnodactyly in the family.

From 1935 to 1945 the patient was employed as recreational director of the Country Home for Crippled Children (University of Chicago). On two occasions during this period routine examinations demonstrated the presence of cardiac enlargement (70 per cent oversize) and a harsh basal systolic murmur. The blood pressure was 118 systolic and 66 diastolic. The only symptom, exertional dyspnea, was a minor one and never interfered with the patient's work or activities. She attended night school and completed most of the courses required for a bachelor's degree. In September 1945 she complained of scotoma in the left visual field. The retina became completely detached despite two attempts to refix it by microcoagulation, and within a short time total blindness ensued.

In the spring of 1946 she made plans to obtain a seeing-eye dog and was advised that she would be required to walk for an hour at a pace of three and one-half miles per hour. She began training to increase her tolerance to exercise. On the morning of May 4, 1946, she walked vigorously, returning home breathless. That afternoon at 4 p. m., while scrubbing the floor, she had sudden severe, constricting precordial pain without radiation and fainted. Unconsciousness persisted for five minutes. When revived, she became nauseated and vomited. Dyspnea appeared and became intense. She noted a tingling sensation in the fingers of her left hand. When admitted to Billings Hospital at 8 p. m. she was pale and extremely dyspneic. The pulse, though feeble, was regular at 66 per minute. The blood pressure was 100 systolic and 45 diastolic. A few crepitant rales were heard in the left pulmonary field. Inspection disclosed a heaving precordium, and percussion demonstrated massive cardiac enlargement. There was a harsh systolic thrill and murmur, of greatest intensity in the second and third left interspaces. The liver was barely palpable in a scaphoid abdomen. Intranasal administration of oxygen, sedation and complete rest in bed were ordered. The laboratory findings were as follows: hemoglobin content, 13 Gm.; red blood cells 4,720,000; white blood cells 14,050,

small size of the gray-white right optic nerve was the only gross abnormality. The body of the sacrum was a hollow shell filled by a thin-walled sac containing spinal fluid. Two fluid-filled sacs protruded through symmetric, 5 cm. size openings in the anterior sacral surface.

Microscopic Examination: The aortic medial changes were most outstanding in the region of the perforation but were easily detectable in all portions of both the thoracic and the abdominal aorta (fig. 7). The basic lesions were similar in all respects to those found in case 1. The plane of dissection in the aorta and its



Fig. 5.—Close view of the aortic laceration, which lies at the upper border of the dilated sinuses of Valsalva (case 2). Note the bulging wall about the right coronary ostium.

branches was close to the adventitia, and only a small portion of media remained with the outer layer. The myocardial fibers were hypertrophic, and small scars were seen in relation to collagenous septums. The infarct was obviously a fresh one, showing hemorrhage, incomplete necrosis of muscle fibers and little or no cellular infiltration. The leaflets of the tricuspid, mitral and aortic valves were thickened by myxomatous fibrous tissue. The mitral valve ring was calcified, and the adjacent myocardium contained dense hyaline scars. The endocardial surface

aorta. The emptied heart weighed 590 Gm. The right atrium had a thick wall, and the auricle contained a small thrombus. The foramen ovale was closed. The dilated tricuspid orifice measured 14 cm., and the valve leaflets were thick and nodular. The distended and hypertrophied right ventricle had a firm wall 5 to 6 mm. thick. The pulmonary valve and the pulmonic trunk were normal. The endocardial surface of the dilated left atrium was gray-white and opaque, with a rough wrinkled area just above the anterior mitral leaflet (fig. 4). The mitral orifice was enlarged, measuring 13.5 cm. The leaflets and chordae tendineae were thick, gray-white and firm. The left ventricle was roomy but had a thick wall which measured 20 mm. near the base. The myocardium contained a large area of softening in the posterior-superior portion of the septum and the posterolateral wall of the left ventricle. The endocardial surface of the infarct was red-yellow, and the sectioned surfaces were hemorrhagic. The aortic orifice measured 8 cm., and its leaflets were fused and thick, with large nodules of Arantius. The left coronary artery was patent. A transverse tear, 2.5 cm. in length, was located 3.5 cm. above the aortic valve



Fig. 4.—Fibrous thickening of the mitral valve and left atrial endocardium (case 2).

(fig. 5). Blood forced through this intimal tear had dissected the media. The false passage included two thirds of the circumference of the aorta. It extended proximally to the aortic valve ring and peripherally to the iliac arteries. The dissection involved the wall of the right coronary artery. The inner medial layer of this artery was avulsed from a thin outer layer, and the space between was filled by a blood clot (fig. 6). The false passages in the innominate, superior mesenteric and right iliac arteries contained blood clots, while those in the left carotid and subclavian arteries contained fluid blood. The right renal and inferior mesenteric arteries were torn away from the inner wall and communicated only with the lumen of the dissecting aneurysm.

The right pleural cavity was twice the size of the left because of the severe kyphoscoliosis and the cardiac enlargement. The lower lobe of the left lung was compressed. The middle lobe of the right lung was rudimentary, consisting of a single lobule. Both lungs were congested and wet. The brain weighed 1,250 Gm. The

lax. Many of them showed an irregularly wavy or helical pattern. The lens capsule was thin, exceptionally so posteriorly. The lens substance was distorted by swelling and fragmentation of the subcapsular fibers posteriorly and by equatorial subcapsular clefts. Its inferonasal equatorial sector was rounded and drawn upward and toward the temple (in the region of the lens coloboma seen during life). The degenerated shrunken vitreous lay displaced forward and included scattered erythrocytes and a few pigment-bearing macrophages. The detached retina was edematous, and it was further distorted by adhesions between folds and by gliosis at the margin of an old tear. It overlay pools of protein-rich fluid. A tract of vascular reparative tissue extended from the ora serrata to a region on the temporal side of the macula. The choroid and sclera were thinned, especially posteriorly. The optic nerve head was moderately edematous. It had a connective tissue-covered meniscus and was

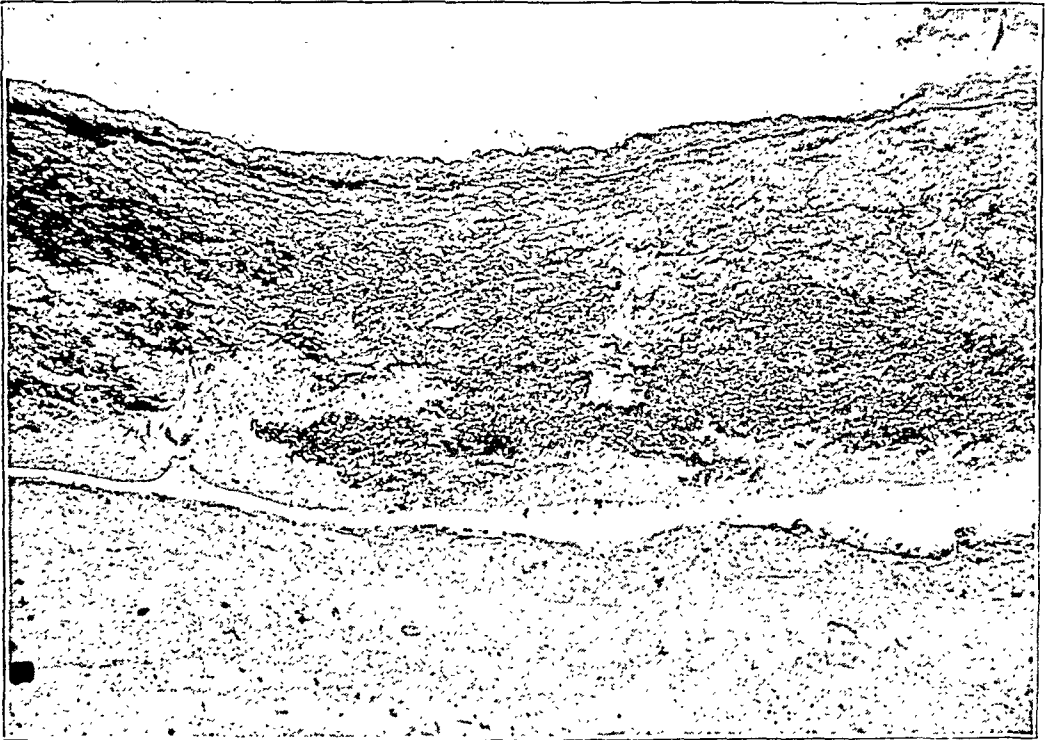


Fig. 7.—Aortic cystic medionecrosis and dissecting aneurysm (case 2). The dissection channel is close to the adventitial border. Weigert's stain for elastic fibers; $\times 55$.

ringed by a zone of choroidal fibrosis. This zone contained few blood vessels, no pigment elements and no remnants of the glassy membrane.

Anatomic Diagnosis.—The anatomic diagnosis was as follows: arachnodactyly; dissecting aneurysm of the aorta and its main branches; malformation of the aortic media; complete occlusion (due to tamponade by clotted blood in the false passage) of the right coronary artery and partial occlusion of the innominate, superior mesenteric and right iliac arteries; communication of the right renal and inferior mesenteric arteries with the dissecting aneurysm, secondary to avulsion of their ostiums from the inner wall of the false passage; acute myocardial infarction; cardiac hypertrophy; fibromyxomatous thickening of the tricuspid, mitral and aortic valves and of the left atrial endocardium; vestigial middle lobe of the right lung; atelectasis of the lower lobe of the left lung; atrophy of the thyroid; diffuse increase in

of the left atrium was thickened and thrown into verrucous folds composed of loose cellular connective tissue. These changes were not of the type seen as sequelae in rheumatic fever. The media of the pulmonary artery contained an excess of irregularly arranged muscle fibers.

There was an apparent preponderance of eosinophilic cells in the anterior pituitary. The thyroid was composed of small acini, half of which contained a normal amount of colloid. Groups of acini were separated by thick fibrous trabeculae infiltrated by lymphocytes. The other endocrine glands, the thymus and the generative organs were normal. Renal tubules contained many blue-staining (calcified) casts. The bone marrow was hyperplastic, with incomplete maturation of myeloid elements. There was passive congestion of the lungs, liver and spleen. The brain was normal.

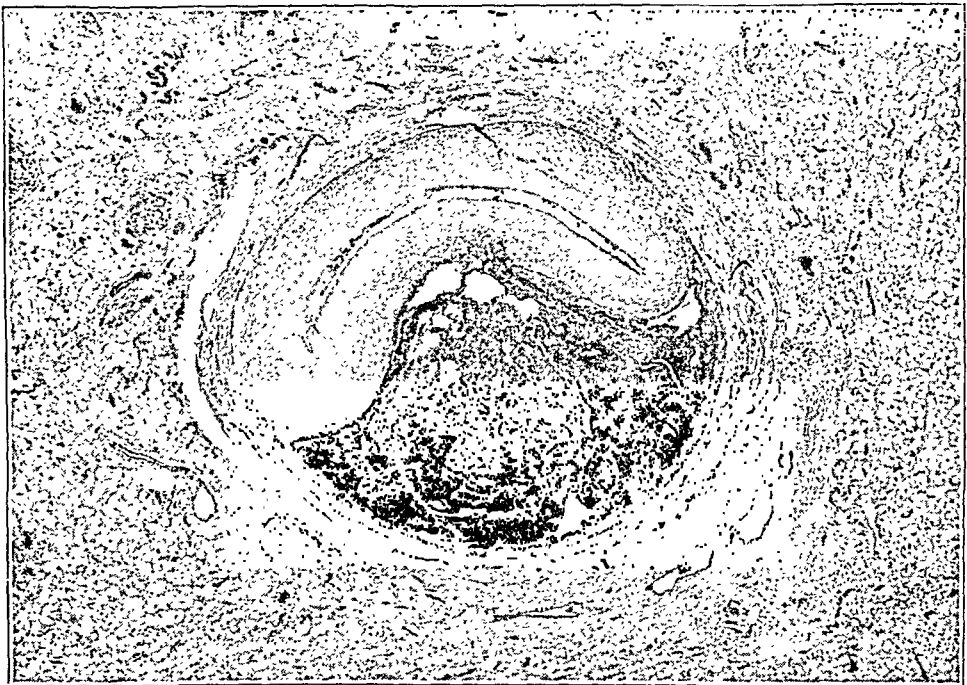


Fig. 6.—Freshly clotted blood in the dissecting aneurysm, occluding the right coronary artery by tamponade (case 2). Hematoxylin and eosin stain; $\times 20$.

Left Eye:¹⁴ The eyeball was irregularly ovoid, measuring 25.5 mm. transversely, 26.5 mm. vertically and 28 mm. in the anteroposterior axis. The posterior segment appeared elongated and terminated in a small posterior staphyloma. The sclera was thin, and the retina was completely detached except at the ora serrata and the disk margin.

Histologic Examination: The conjunctiva and all layers of the cornea were normal. The canals of Schlemm were open, but only vestiges of Fontana's spaces were present in the rather compact meshwork of the iris angle. The iris was normal, but the ciliary muscle was attenuated, as is usual in high grade myopia. The much shrunken ciliary processes were directed posteriorly, and their epithelium had lost much of its pigment. The zonular fibrils supporting the lens were scanty and

14. The pathologic description was given by Dr. C. Keith Barnes

hearts of normal infants and on the valves of hearts with congenital lesions. It seems probable that these endocardial lesions are manifestations of a developmental defect.

Changes in the aortic media resembling the lesions which we have described have been reported previously in 2 patients with arachnodactyly by Baer, Taussig and Oppenheimer.⁵ These authors concluded that they were the result of a congenital abnormality. Detailed histologic descriptions of the aorta are lacking in the other 10 case reports. The conclusion that the aortic medial lesions in Marfan's syndrome are the result of a congenital defect seems reasonable, but it must be admitted that these lesions are indistinguishable from "medionecrosis aortae idiopathica cystica" described by Erdheim.¹⁶ This author and Rottino¹⁷ have stressed the peculiarities of this type of aortic medionecrosis, particularly the abundance and abnormal arrangement of smooth muscle fibers, which they attributed to reparative hyperplasia. The derangement of the smooth muscle fibers, the rarefaction, fragmentation and distorted pattern of elastic lamellas and the presence of mucoid-filled cystic spaces are distinctive characteristics of this aortic medial lesion. In most instances it has been reported (Erdheim and others) in middle-aged and elderly persons with a history of hypertension. It seems incredible that the similar lesions found at necropsy in such a high proportion of non-hypertensive adolescents and young adults with arachnodactyly are of identical origin. However, it is not possible at this time to confirm or deny that the aortic medionecrosis in Marfan's syndrome is of a developmental nature, nor can the true incidence and importance of the aortic lesions be evaluated from existing data on necropsies. The aortas of all persons with Marfan's syndrome should be examined carefully whether or not they exhibit unusual gross changes. The possibility of formes frustes of Marfan's syndrome should be considered whenever dissecting aneurysm or unexplained widening of the ascending aorta is suspected clinically or found at autopsy.

The possible role of the endocrine glands in Marfan's syndrome has been debated repeatedly. There is no anatomic evidence to implicate any of them but the hypophysis. In cases 1 and 2 the hypophysis appeared to contain more than the usual proportion of eosinophilic cells. Weill¹⁵ made the same observation in an adult, and Salle,¹² Börger¹⁸ and Bergstrand¹⁹ found a similar change in infants. No increase of

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19. Bergstrand, C. G.: Beitrag zur pathologischen Anatomie der Arachnodaktylie, mit Bericht über einen eigenen Fall, *Acta pædiat.* **30**:345-363, 1943.

eosinophilic cells in the hypophysis; congenital anterior sacral meningocele; absence of the right eye, with atrophy of the right optic nerve; congenital and acquired defects of the left eye, and passive congestion of the lungs, liver and spleen.

COMMENT

Dissecting aneurysm of the aorta is reported in 2 adults with Marfan's syndrome. The first patient had been seen once prior to death. There were loud systolic and soft diastolic murmurs heard, with greatest intensity in the aortic area. A high pulse pressure was the only other clinical sign of aortic regurgitation recorded. The postmortem examination revealed cardiac hypertrophy, dilatation of the aortic orifice, displacement of the coronary ostia upward and fusiform dilatation of the ascending aorta. Death resulted from perforation of this aneurysm by dissection into the pericardial sac. The second patient was observed at intervals for fifteen years. She had a harsh systolic murmur and thrill, of greatest intensity in the second and third left interspaces. She was believed to have congenital heart disease, with interventricular septal defect, but the cardiac signs were attributed in part to thoracic deformity. In her terminal illness the severe pain in the back and the absence of pulsation at the left wrist were important but disregarded clues to the diagnosis of dissecting aneurysm. The postmortem examination revealed an extensive dissecting aneurysm of the aorta. A unique finding was the extension of the dissection into the right coronary artery, with occlusion resulting from compression of the artery by a blood clot in the false passage. Death resulted from myocardial infarction rather than from rupture of the aneurysm. In both cases histologic examination of the aorta disclosed an identical malformation of the aortic media.

These 2 cases together with 4 previously reported¹⁵ make a total of 6 in which there were aortic lesions in the fourteen necropsies performed on patients who had had arachnodactyly. These figures are highly significant if it is considered that 5 of the 8 patients with no described aortic lesions were under 28 months of age, while those with aortic lesions were between 14 and 35 years (table). The gross descriptions of the hearts and aortas are similar in the 6 cases. The lesions include cardiac hypertrophy, deformities of the aortic valve, dilatation of the aortic valve ring and varying degrees of dilatation of the sinuses of Valsalva and/or of the ascending portion of the aorta. Mural and valvular thickenings grossly resembling rheumatic lesions were seen in each case.

The endocardial changes in our cases proved not to be the rheumatic changes suspected grossly. The valves were thickened by myxomatous tissue similar to the gelatinous nodules often seen on the valves of the

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EFFECTS ON THE CARDIOVASCULAR SYSTEM OF FLUIDS ADMINISTERED INTRAVENOUSLY IN MAN

V. Function of Cutaneous Capillaries and Lymphatic Vessels

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EARLIER studies from this and other laboratories¹ have yielded data on the nature of the changes in the dynamics of the circulation in patients receiving infusions of electrolytes intravenously. All authors agree that such infusions increase blood volume, raise venous and intra-auricular pressures and increase cardiac output; changes in arterial pressure are variable. There are, however, no data available

From the Medical Service and Medical Research Laboratories, Beth Israel Hospital, and the Department of Medicine, Harvard Medical School.

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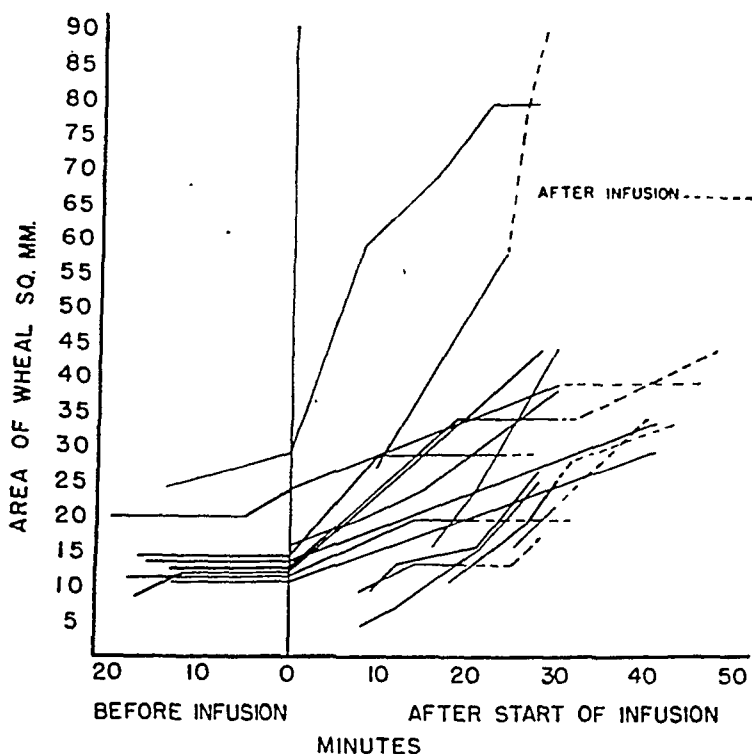
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eosinophilic cells was found in 5 other cases. Hormonal studies have been few, and none of the existing evidence clarifies the role of the hypophysis.

SUMMARY

The clinical characteristics of Marfan's syndrome are discussed, particularly as manifested in adults. The significant lesions observed in twelve autopsies, seven of which were performed on adolescents or adults, are tabulated. Cardiovascular lesions are common and especially important. They include aortic medial necrosis and endocardial lesions which simulate those of rheumatic fever. The former is the more dangerous, resulting in dilatation of the aortic valve ring, the sinuses of Valsalva and the ascending portion of the aorta. Death may occur suddenly from dissecting aneurysm and rupture of the aorta. The role of the endocrine glands, particularly the hypophysis, remains obscure. Clinical data and complete data on the necropsies are presented for 2 adults with arachnodactyly, both of whom died as the result of dissecting aneurysm of the aorta.

950 East Fifty-Ninth Street.



Increase in size of cutaneous wheals during intravenous infusions.

Results of Intravenous Infusion of Fluids in Eight Patients

Case	Solution Infused	Average Rate of Infusion, Cc./Min.	Venous Pressure, Cm. of Water		Percentage Increase in Area of Wheal		Site of Wheal
			Before Infusion	At End of Infusion	Before Infusion	During Infusion	
G	5% dextrose in isotonic solution of sodium chloride	60	2.4	13.6	1) 52 2) — 3) —	250 50 178	Same arm as infusion Same arm as infusion Same arm as infusion
A	5% dextrose in isotonic solution of sodium chloride	60	7.4	11.8	1) 0 2) —	172 115	Arm opposite to infusion Arm opposite to infusion
E	5% dextrose in isotonic solution of sodium chloride	80	9.7	15.7	1) 0 2) —	98 556	Same arm as infusion Same arm as infusion
P	Isotonic solution of sodium chloride	60	5.6	12.7	1) 21 2) —	62 145	Thigh Thigh
W	Isotonic solution of sodium chloride	85	7.3	14.6	1) 0 2) —	56 92	Shoulder of same arm as infusion Shoulder of same arm as infusion
T	Isotonic solution of sodium chloride	60	8.4	17.0	1) 15 2) 15 3) — 4) —	157 202 66 225	Same arm as infusion Arm opposite to infusion Same arm as infusion Arm opposite to infusion
C	Isotonic solution of sodium chloride	75	1.0	6.7	19	137	Same arm as infusion

on changes in the function of small vessels during the course of intravenous infusions in man, and it was therefore considered of interest to make the present study.

MATERIAL AND METHODS

Seven men, 16 to 58 years old, were studied; none had any evidence of cardiovascular disease. Each received an infusion into an antecubital vein of 1,800 cc. of isotonic solution of sodium chloride or 5 per cent dextrose in isotonic solution of sodium chloride; the rates of infusion were between 60 and 85 cc. per minute (table).

The venous pressure was measured by means of the method of Moritz and von Tabora,² and lymphatic function was studied by means of a method suggested by Griffith and others³; after cleansing of the skin with xylene, the capillaries of the finger nail fold were observed under oil by means of a microscope with a magnification of 100 or 200 times.

OBSERVATIONS

Capillary Flow.—Before the beginning of the infusion, the capillaries of the finger nail fold were normal in appearance in every patient; they were visible in only small numbers, and flow in them was slow. No change was observed until several hundred cubic centimeters of fluid had been given intravenously. Thereafter, additional capillary loops became visible. All visible vessels were wider than normal, and blood flow was greatly accelerated; in some instances the capillaries were seen to pulsate markedly. These changes were progressive and became maximal usually before, but occasionally after, the end of the period of infusion of fluid, i.e., when 1,000 to 1,800 cc. had been given. Thereafter, the findings remained unchanged until the intravenous infusion was ended. Within a few minutes after the termination of the infusion the degree of change from the normal in the capillaries became less, and over a period of twenty to forty minutes most or all of the change disappeared.

Lymphatic Function.—Wheals containing dye showed no increase or only small increases in size in fifteen to twenty minute periods be-

IX. The Treatment of Shock with Concentrated Human Serum Albumin; Preliminary Report, *ibid.* **23**:506, 1944. (i) Fletcher, A. G.; Hardy, J. D.; Riegel, C., and Koop, C. E.: Gelatin as a Plasma Substitute: The Effect of Intravenous Infusion of Gelatin on Cardiac Output and Other Aspects of the Circulation of Normal Persons, of Chronically Ill Patients, and of Normal Volunteers Subjected to Large Hemorrhage, *ibid.* **25**:405, 1944.

2. Moritz, F., and von Tabora, D.: Ueber eine Methode beim Menschen den Druck in oberflächlichen Venen exakt zu bestimmen, *Deutsches Arch. f. klin. Med.* **98**:475, 1910.

3. Griffith, J. Q.; Roberts, E.; Rutherford, R. B., and Corbit, H. O'B.: Studies of Criteria for Classification of Arterial Hypertension: III. Cutaneous Lymphatic Flow, *Am. Heart J.* **21**:62, 1941.

sion is of interest in relation to possible differences in the effects of infusions on patients with cardiac edema and on those with nephritic edema. In the latter lymphatic function is greatly accelerated,⁷ and it is probable therefore that extravasated fluid reenters the circulation readily; a strong tendency toward the development of pulmonary edema exists in such patients. In patients with cardiac edema, on the other hand, lymphatic function is impaired,⁷ and presumably extravasated fluid tends to remain in the tissues; many patients with cardiac disease tolerate infusions of isotonic solutions of sodium chloride remarkably well.⁶

The fact that evidence of loss of fluid from the circulation exists in patients receiving infusions of solutions of electrolytes is also of clinical interest. The two tissues of greatest water content are the skin and the pulmonary parenchyma. Accumulation of fluid consequent to increased filtration from the circulation is presumably greatest in these two tissues. Large volumes of fluid may exist in the skin without causing symptoms and without being detectable by clinical examination. In the case of the lungs, however, the accumulation of excessive fluid may precipitate respiratory signs and symptoms. Accordingly, it is not surprising that in patients in whom pulmonary edema is latent because of the presence of cardiac or pulmonary disease, uremia, disorders of the central nervous system or other conditions overt manifestations of that disorder may be caused during or after the intravenous infusions of a solution of electrolytes.

SUMMARY AND CONCLUSIONS

Capillary microscopy reveals a progressive dilatation of the small blood vessels of the finger nail fold during intravenous infusions; blood flow is greatly accelerated. Cutaneous lymphatic flow is greatly increased during intravenous infusions of solutions of electrolytes, apparently as a consequence of the loss of fluid from the circulation.

7. McMaster, P. D.: The Lymphatics and Lymph Flow in the Edematous Skin of Human Beings with Cardiac and Renal Disease, *J. Exper. Med.* **65**: 373, 1937.

fore the start of the infusion; the increases in area ranged from 0 to 52 per cent and averaged 15 per cent (table and figure). During the infusion, wheals previously made and newly made wheals increased in area by 50 to 556 per cent; the average increase was 160 per cent (table and figure). The location of the wheals did not appear to influence the degree of increase. In most instances streamers radiating out from the wheals appeared during the infusions of fluid intravenously; these ranged in length up to 6 mm. No correlation was found between the increase in size of the wheals in the skin and the rise in venous pressure induced by the infusion (table).

COMMENT

More than seventy years ago von Lesser,⁴ after studies of the effects of transfusions on dogs, concluded that "the excess of blood accumulates principally in the small vessels." The conclusion that the final adjustment of the circulation to an intravenous infusion was a progressive dilatation of small blood vessels was subsequently restated by Meek and Eyster⁵ and Altschule and Gilligan.^{1b} The present work supports these earlier conclusions and in addition corroborates the direct observations of Meek and Eyster on the capillaries of the omentum of dogs receiving infusions.

The enormous distensibility of the finest portions of the vascular bed is well known. When, however, the vascular bed is overdistended, as in patients with chronic congestive failure, severe pulmonary disease or polycythemia vera, compensation for increases in blood volume consequent to intravenous infusions is impaired; the venous pressure rises abnormally, and untoward symptoms may occur.⁶

The present observations, which indicate an increase in lymphatic flow during intravenous infusions of solutions of electrolytes, are in harmony with the concept that such fluids leave the circulation rapidly and that only a portion of the volume given can be found in the circulation at the end of the period of infusion.^{1a} The loss of fluid from the circulation is probably the consequence of an increased filtering pressure and also of expansion of the filtering bed. On the other hand, the increase in activity of the lymphatic vessels indicates that some of the extravasated fluid is returned to the circulation. This last conclu-

4. von Lesser, L. *Surgical Emergencies*, New York, Bermingham and Co., 1883, pp. 13-17.

5. Meek, W. J., and Eyster, J. A. E.: The Effect of Plethora and Variations in Venous Blood Pressure on Diastolic Size and Output of the Heart, *Am. J. Physiol.* **61**:186, 1922.

6. Richards, D. W., Jr.; Caughey, I. L.; Cournand, A., and Chamberlain, F. L.: Intravenous Saline Infusion as a Clinical Test for Right-Heart and Left-Heart Failure, *Tr. A. Am. Physicians* **52**:250, 1937.

definite diagnosis but was presumptively diagnosed as pulmonary tuberculosis, inactive or arrested.

Palmer's report¹ on nontuberculous pulmonary calcification and sensitivity to histoplasmin and the epidemiologic study of pulmonary lesions in Ohio by Olsen, Wright and Nolan² indicated that a study of the sensitivity of the skin to histoplasmin in these patients might offer a solution to the problem. Christie³ has already shown that pulmonary calcifications do exist in certain young persons who apparently have not had tuberculosis. These persons frequently exhibit sensitivity of the skin to histoplasmin.

It is well known that many of the fungus infections show a cross sensitivity reaction. Injections of histoplasmin, coccidioidin, haplosporangin and blastomycin produce cross reactions that have been clearly demonstrated in animals.⁴

METHOD OF STUDY

The cutaneous tests were done in a battery of three, with a control of the diluting fluid. The following antigens were given: (1) tuberculin—0.00002 mg. of purified protein derivative in 0.1 cc. of fluid, (2) coccidioidin (C. E. Smith)—1 to 1,000 dilution in 0.1 cc. of fluid and (3) histoplasmin (Army Institute of Pathology)—1 to 1,000 dilution in 0.1 cc. of fluid. All tests were made on the left arm at the same time by one technician. The same technician read the results by measuring the area of induration and erythema. Any area of less than 5 by 5 mm. was considered to indicate a negative reaction, and the second strength solutions were used as follows: (1) tuberculin—0.005 mg. of purified protein derivative in 0.1 cc. of fluid, (2) coccidioidin—1 to 10 dilution in 0.1 cc. of fluid and (3) histoplasmin—1 to 10 dilution in 0.1 cc. of fluid. All tests were given intradermally in the manner prescribed for administration of the tuberculin test.

Cultures were planted in duplicate sets. One set remained at room temperature, and the other was incubated at 37 C. Both sets were held for six weeks before being reported as sterile. Each set consisted of: (1) beef infusion broth tubes, (2) Sabouraud's agar slants, (3) corn meal agar slants and (4) blood agar slants. The technic was good. Only two contaminants occurred in over one hundred and twenty sets.

To correlate epidemiologic, clinical, roentgenologic and laboratory data, a form was prepared indicating the state of birth, countries and states visited, roentgenologic characteristics of pulmonary lesions, physical condition and the history

1. Palmer, C. E.: Non-Tuberculous Pulmonary Calcifications and Sensitivity to Histoplasmin, *Pub. Health Rep.* **60**:513-520, 1945.

2. Olsen, B. J.; Wright, W. H., and Nolan, M. O.: An Epidemiological Study of Calcified Pulmonary Lesions in an Ohio County, *Pub. Health Rep.* **56**: 2105-2126, 1941.

3. Christie, A., and Peterson, J. C.: Pulmonary Calcifications in Negative Reactors to Tuberculin, *Am. J. Pub. Health* **35**:1131, 1147, 1945.

4. Emmons, C. W.; Olsen, B. J., and Eldridge, W. W.: Studies of the Role of Fungi in Pulmonary Disease, *Pub. Health Rep.* **60**:1383-1394, 1945. Smith, C. E.: Coccidioidomycosis, *M. Clin. North America* **27**:790-807, 1943.

SENSITIVITY OF SKIN TO HISTOPLASMIN IN DIFFERENTIAL DIAGNOSIS OF PULMONARY DISEASE

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DURING the period of rapid demobilization of the United States Army following cessation of hostilities, many soldiers were found to have roentgenologic evidence of pulmonary pathema. This was discovered at routine physical examination during the process of their separation from the Service. More than 1,500 patients were sent to the Moore General Hospital from various separation centers over the country because of roentgenologic evidence of pulmonary disease. Most of them were asymptomatic. Their sputum on repeated examinations was negative for acid-fast organisms in more than 50 per cent of the cases. Of the total number, 3.5 per cent had a negative reaction to the cutaneous test for tuberculin. For the most part, these patients were to be observed for a period of at least six months. This period of observation was necessary to determine the presence of activity. All patients were considered to have pulmonary tuberculosis until it was proved otherwise. The disease was considered to be active until the men were observed for six months, after which the men were classified, and when their condition was arrested they were discharged from the Service in compliance with existing directives.

It is apparent that this was a difficult diagnostic problem. Some of the patients were proved to have coccidioidomycosis on examination of the sputum and by positive reactions to the complement fixation test and the precipitin tests. In others the condition was never given a

From the Moore General Hospital, Swannanoa, N. C.

the diagram. Parts *B* and *C* give similar information for sensitivity to histoplasmin and coccidioidin.

It has been noted that in practically every instance in which a strongly positive reaction (20 mm. and over) was obtained to histoplasmin in the first strength, a weakly positive reaction (5 to 10 mm.) was obtained to coccidioidin in the second strength. Similarly, a strong positive reaction (20 mm. and over) to coccidioidin in the first strength was usually accompanied with a mild reaction to histoplasmin in the second strength (5 to 10 mm.).

Of the 1,220 patients studied, only 528 were followed for a sufficient length of time to complete the clinical observations. Of the 528, 117

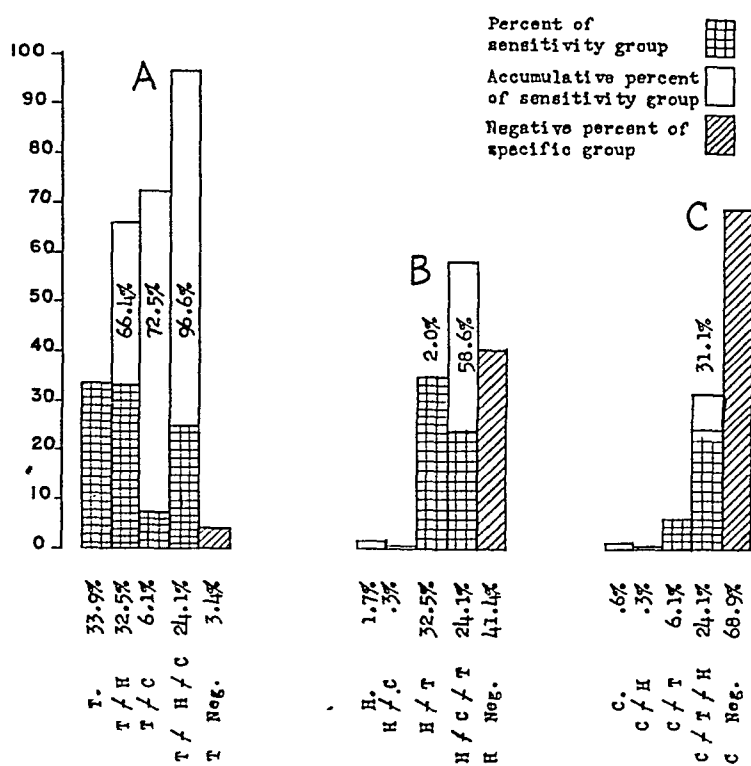


Fig. 1.—Bar diagram showing relative frequency of sensitivity of the skin to tuberculin (*T*), coccidioidin (*C*) and histoplasmin (*H*). Cross-hatched bars indicate the specific combinations in which sensitivity occurred. The open bars show the accumulative specific sensitivity to each antigen as influenced by adding various sensitivity groups as indicated at the base of each bar.

were ultimately found to have acid-fast bacilli in their sputum. The few patients with anemia responded well to iron and vitamin therapy. The hemoglobin content, the white blood cell count and the temperature varied so greatly that a statistical study of these factors was considered to be of no value.

The factors considered to be of most importance in the study are given in table 2. Here, certain roentgenologic findings together with the physical symptoms and a history of pain in the chest and of previous attacks of pleurisy are recorded for the three sensitivity groups. The

of previous pulmonary diseases. In addition, on all patients showing strongly positive reactions to histoplasmin biopsies of lymph nodes and aspirations of sternal marrow were carried out for culture and histologic examination.

RESULTS OF THE STUDY

A total of 1,220 persons were tested. Table 1 shows the distribution of tests with respect to the degree of sensitivity and the combinations

TABLE 1.—*Sensitivity of the Skin by Sensitivity Groups Showing Degree of Reaction by Area of Induration*

	Area of Induration							Total	No. of Persons
	5-10 Mm.	10-20 Mm.	20-30 Mm.	30-40 Mm.	40-50 Mm.	50-60 Mm.	60-70 Mm.		
Group 1.....	293
Tuberculin.....1st	86	133	34	14	2	..	1	270	
2d	4	7	4	7	1	23	
Coccidioidin.....1st	136	20	5	2	163	
2d	94	28	4	2	2	130	
Histoplasmin.....1st	123	46	2	1	1	173	
2d	60	43	8	2	1	..	1	120	
Group 2.....	75
Tuberculin.....1st	29	19	5	2	55	
2d	3	10	3	2	2	20	
Coccidioidin.....1st	23	8	31	
2d	29	12	2	1	44	
Group 3.....	397
Tuberculin.....1st	138	114	33	6	1	292	
2d	14	55	26	8	1	1	..	105	
Histoplasmin.....1st	140	23	3	1	167	
2d	110	91	21	3	6	230	
Group 4.....	4
Coccidioidin.....1st	1	1	
2d	2	1	3	
Histoplasmin.....1st	1	1	
2d	2	1	3	
Group 5.....	413
Tuberculin.....1st	86	118	16	5	225	
2d	25	77	60	20	2	1	3	188	
Group 6.....	7
Coccidioidin.....1st	
2d	2	2	2	1	7	
Group 7.....	21
Histoplasmin.....1st	2	2	4	
2d	6	8	2	17	
Total number of persons.....									1,220

of sensitivity which occurred. It is apparent from this table that by far the largest number showed only a mild reaction to histoplasmin, the area being under 15 mm. in diameter. The patients were grouped according to sensitivity to each of the three antigens. This grouping is shown by the bar diagrams in figure 1, *A* showing the percentage of patients sensitive to tuberculin by sensitivity groups. The open bars show the accumulative percentage of sensitivity to tuberculin as influenced by adding patients with sensitivity combinations as indicated in

total number of clinical factors are tabulated, and the number occurring in each sensitivity group is recorded as a percentage of the total number for each factor in the entire group. The expected number of factors, if not influenced by sensitivity of the skin, should parallel roughly the percentage for each sensitivity group, which is 93 per cent for tuberculin, 48 per cent for histoplasmin and 30 per cent for coccidioidin as related to the whole number of 528. By subtraction of the observed percentage of factors from the expected percentage, the difference is obtained for each factor in each sensitivity group.

While there was a statistically significant difference between the occurrence of pulmonary calcifications in the group with sensitivity to histoplasmin, it must be remembered that many of the patients were

TABLE 3.—*Anatomic Location of Pulmonary Calcifications with Respect to Sensitivity to Tuberculin, Histoplasmin and Coccidioidin*

Antigen	Total No. of Patients with Calcifications	Patients with Pulmonary Calcifications, %	Multiple Hilar Calcifications	Single Hilar Calcifications	Patients with Hilar Calcifications, %	Multiple Parenchymal Calcifications	Single Parenchymal Calcifications	Patients with Parenchymal Calcifications, %
Tuberculin only (209)....	44	15.3	12	4	5.52	22	6	13.4
Tuberculin and coccidioidin (38).....	12	31.6	3	1	10.5	5	3	21.0
Tuberculin and histoplasmin (127).....	50	39.3	16	1	13.4	21	12	26.0
Tuberculin, coccidioidin and histoplasmin (117)	44	34.6	10	7	14.5	15	12	23.0
Coccidioidin only (4)....	1	25.0	0	0	0.0	1	0	25.0
Histoplasmin only (10)...	7	70.0	2	0	20.0	3	2	50.0
Coccidioidin and histoplasmin (2).....	2	100.0	0	0	0.0	1	1	100.0
All tests negative (21)...	7	33.3	3	1	19.3	2	1	14.3
Total.....	167		46	14		70	37	

also sensitive to tuberculin and coccidioidin, as shown in the bar diagram in figure 1. For this reason it is difficult to make a definite statement. However, it is evident that the group of patients with sensitivity of the skin to histoplasmin showed a higher percentage of pulmonary calcifications than a similar group of patients with sensitivity of the skin to tuberculin. That is to say, the percentage of the 528 patients with sensitivity to histoplasmin (48 per cent) included 62 per cent of the patients with pulmonary calcifications in the parenchyma and 60 per cent of the patients with hilar calcification. Of the 528, 93 per cent were sensitive to tuberculin, and this number included 90 per cent of the patients with hilar calcification and 98 per cent of the patients with parenchymal calcifications. Of 10 patients who were sensitive to histoplasmin and not to tuberculin and coccidioidin, 7, or 70 per cent, had pulmonary calcifications. Table 3 shows the distribution of 167 patients with pulmonary calcifications.

TABLE 2.—*Clinical and Roentgenologic Observations Among Five Hundred and Twenty-Eight Patients with Respect to Sensitivity to Tuberculin, Histoplasmin and Coccidioidin*

Clinical Factors Occurring in 528 Patients	Sensitivity to Tuberculin (491, or 93%)					Sensitivity to Histoplasmin (256, or 48%)					Sensitivity to Coccidioidin (161, or 30%)				
	No. of Patients	2	3	4	Column 3 Minus Column 4	Percentage Expected of Total Occur- rence	No. of Patients	6	7	Percentage Expected of Total Occur- rence	Column 7 Minus Column 8	No. of Patients	10	11	Percentage Expected of Total Occur- rence
Roentgenologic lesion, dif- fuse.....	339	310	91.5	93.0	-1.5	93.0	109	49.7	48.0	+1.7	93	30.0	27.4	30.0	-2.6
Roentgenologic lesion, dis- crete.....	186	171	92.0	93.0	-1.0	93.0	90	47.4	48.0	-0.6	53	30.0	31.1	30.0	+1.1
Hilar calcifications.....	60	54	90.0	93.0	-3.0	93.0	36	60.0	48.0	+12.0	21	30.0	35.0	30.0	+5.0
Parenchymal calcifica- tions.....	107	96	98.7	93.0	+5.7	93.0	76	62.6	48.0	+14.6	38	30.0	35.5	30.0	+5.5
Fibrotic lesion.....	419	380	90.7	93.0	-2.3	93.0	202	47.2	48.0	-0.8	125	30.0	29.9	30.0	-0.1
Exudative lesion.....	344	323	93.7	93.0	+0.7	93.0	180	52.3	48.0	+14.3	115	30.0	33.4	30.0	+3.4
Cavitation.....	164	152	92.8	93.0	-0.2	93.0	70	48.1	48.0	-0.1	46	30.0	28.0	30.0	-2.0
Pain in upper part of the chest.....	62	50	80.7	93.0	-12.3	93.0	29	46.8	48.0	-1.2	22	30.0	35.1	30.0	+5.4
Pain in lower part of the chest.....	44	31	70.5	93.0	-22.5	93.0	21	42.7	48.0	-5.3	9	30.0	20.1	30.0	-9.6
History of pleuritis.....	61	59	96.7	93.0	+3.7	93.0	14	23.0	48.0	-25.0	9	30.0	16.4	30.0	-13.6
Pleural thickening.....	110	101	92.0	93.0	-1.0	93.0	53	48.3	48.0	+0.3	26	30.0	23.6	30.0	-6.4
Splenomegaly.....	17	16	94.2	93.0	+1.2	93.0	7	41.2	48.0	-6.8	4	30.0	23.5	30.0	-6.5
Hepatomegaly.....	11	9	81.7	93.0	-11.3	93.0	4	36.3	48.0	-11.7	3	30.0	27.3	30.0	-2.7
Lymphadenopathy.....	341	301	88.2	93.0	-4.8	93.0	165	48.5	48.0	+0.5	98	30.0	29.7	30.0	-1.3

the entire 528 patients, both those with negative and those with positive reactions. The points on this map indicate the state in which the patient had lived longest and considered to be his home. It does not necessarily indicate the state of birth or the location of his present home. An effort was made to correlate sensitivity of the skin with the states and foreign countries visited by the patients. This proved to be a hopeless task, as more than 90 per cent of the 528 patients had been in several of the states known to exhibit a high percentage of persons sensitive to histoplasmin.

Sensitivity to histoplasmin has been associated with pulmonary calcifications and, in the fatal cases of histoplasmosis, with involvement of the reticuloendothelial system and enlargement of the spleen, liver

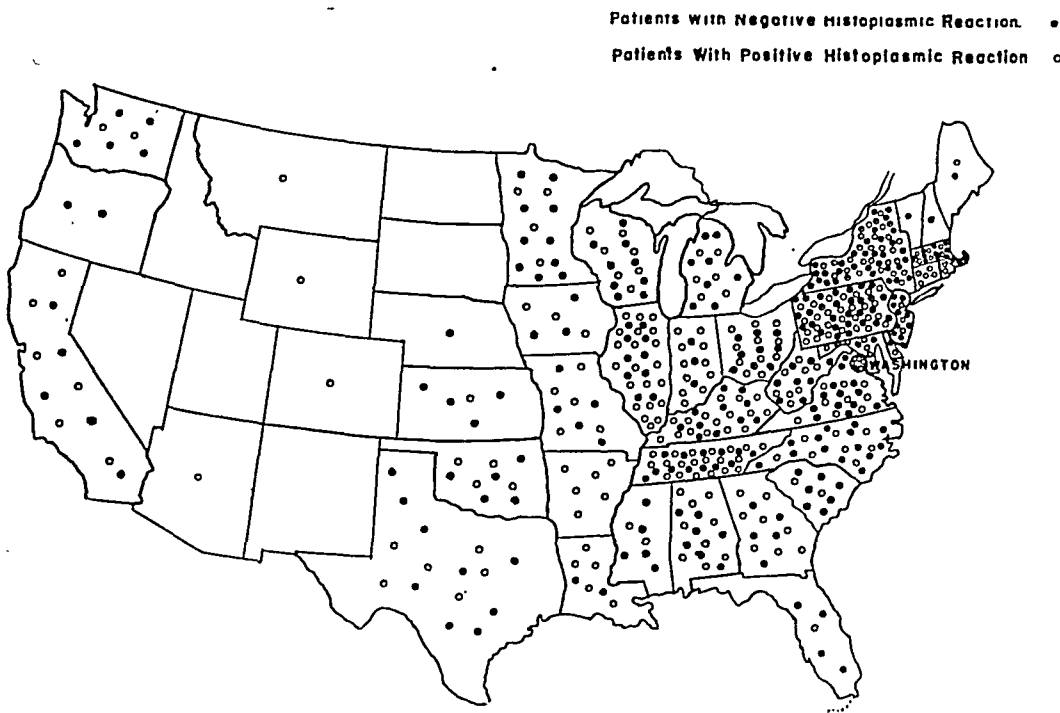


Fig. 2.—Spot map of the United States, showing distribution of 528 cases of pulmonary involvement with respect to sensitivity of the skin to histoplasmin.

and lymph nodes. Christie³ reported the case of a soldier discharged from the Army because of many pulmonary calcifications, with a negative reaction to the tuberculin test and a complete lack of symptoms accompanying a strong sensitivity of the skin to histoplasmin. The calcifications apparently developed during the two year period the soldier was in the Service. In the same article Christie reported the case of a 10 month old boy who died from the results of a bilateral subdural hematoma. Autopsy showed enlarged tracheobronchial lymph nodes, with lesions of multinucleated giant cells lying among large mononuclear cells, surrounded by a zone of endothelial cells. The lesions did not show calcifications or caseations. The hilar nodes showed hyperplasia. The

The 528 patients were studied to determine geographic influence on the incidence of sensitivity to histoplasmin. Recent studies³ would lead to the belief that Tennessee, Virginia, Kentucky, Ohio and Penn-

TABLE 4.—*Tabulation by States of Patients With and Without Sensitivity of the Skin to Histoplasmin and in Relation to Its Combinations with Tuberculin and Coccidioidin*

State	Histo- plasmin Only	Histo- plasmin and Coccidi- oidin	Histo- plasmin and Tuber- culin	Histo- plasmin, Coccidi- oidin and Tuber- culin	Total Number with Positive Reac- tions to Histo- plasmin	Number with Neg- ative Reac- tions to Histo- plasmin	State Total	Percentage of Total Number with Positive Reactions to Histo- plasmin
Alabama.....	4	5	9	7	16	56
Arkansas.....	4	2	6	..	6	100
Arizona.....	1	1	..	1	100
Connecticut.....	1	2	3	2	5	60
California.....	4	2	6	5	11	55
Colorado.....	1	..	1	..	1	100
Delaware.....	1	..	1	1	2	50
Florida.....	1	..	1	4	5	20
Georgia.....	3	5	8	5	13	62
Iowa.....	2	1	3	3	6	50
Idaho.....
Illinois.....	12	9	21	10	31	68
Indiana.....	8	3	11	3	14	79
Kentucky.....	1	..	6	8	15	12	27	56
Kansas.....	1	..	1	4	5	20
Louisiana.....	5	..	5	2	7	71
Mississippi.....	1	1	2	5	7	29
Missouri.....	4	1	5	5	10	50
Massachusetts.....	1	..	4	1	6	13	19	32
Michigan.....	2	4	6	8	14	43
Maine.....	1	..	1	1	2	50
Maryland.....	1	..	2	2	5	3	8	63
Minnesota.....	4	4	10	14	29
Montana.....	1	1	..	1	100
New Jersey.....	1	..	2	..	3	9	12	25
New York.....	1	1	13	11	26	35	61	43
New Mexico.....
North Dakota.....
North Carolina.....	1	..	4	3	8	14	22	36
Nebraska.....	1	1	..
New Hampshire.....	1	1	..
Nevada.....
Oregon.....	2	2	..
Ohio.....	10	1	11	9	20	55
Oklahoma.....	2	2	4	5	9	44
Pennsylvania.....	2	..	14	11	27	29	56	48
Rhode Island.....	2	2	..
South Carolina.....	1	1	2	7	9	22
South Dakota.....
Tennessee.....	2	..	10	8	20	13	33	61
Texas.....	2	4	6	9	15	40
Utah.....
Vermont.....	1	1	..
Virginia.....	3	6	9	13	22	41
Washington.....	2	2	5	7	29
West Virginia.....	5	2	7	9	16	44
Wisconsin.....	1	1	4	1	7	9	16	44
Wyoming.....	1	1	..	1	100
Washington, D. C.....	3	2	5	1	6	83
Honolulu.....	1	1	..	1	100
Canada.....	1

sylvania have the highest percentage of persons with positive reactions. However, table 4 shows that this is not necessarily true. The numbers are too small for the West and Middle West to draw any definite conclusion, but the spot map (fig. 2) indicates the location by state of

TABLE 5.—*Clinical and Roentgenologic Observations on Eighty-One Patients with a Strong Reaction (20 mm. and over) to Histoplasmin Alone and in Combination with Tuberculin and Coccidioidin*

Clinical Factors Occurring in 81 Patients with a Strong Reaction to Histoplasmin	Number of Patients	Sensitive to Histoplasmin (81 Persons, or 100%)			Sensitive to Histoplasmin and Tuberculin (10 Persons, or 49.4%)			Sensitive to Histoplasmin and Coccidioidin (31 Persons, or 42%)			Sensitive to Histoplasmin Only (7 Persons, or 8.6%)		
		Occur- ence, %	Expected Occur- ence, %	Differ- ence	Occur- ence, %	Expected Occur- ence, %	Differ- ence	Occur- ence, %	Expected Occur- ence, %	Differ- ence	Occur- ence, %	Expected Occur- ence, %	Differ- ence
	1	2	3	4	5	6	7	8	9	10	11	12	13
Pulmonary calcifications.....	36	100	100	0	89	49.4	+39.6	31	42	-11	11.1	8.6	+2.5
Exudative lesions.....	69	100	100	0	93	49.4	+40.6	45	42	+3	10.1	8.6	+1.5
Fibrotic lesions.....	51	100	100	0	86	49.4	+36.6	41	42	-1	13.7	8.6	+5.1
Cavitation.....	23	100	100	0	91	49.4	+41.6	65	42	+23	8.6	8.6	0
Lesions of the upper lobe.....	78	100	100	0	89	49.4	+39.6	45	42	+3	8.9	8.6	+0.3
Lesions of the lower lobe.....	11	100	100	0	79	49.4	+29.6	36	42	-6	21.4	8.6	+12.8
Splenomegaly.....	5	100	100	0	100	49.4	+50.6	40	42	-2	0	8.6	0
Hepatomegaly.....	3	100	100	0	100	49.4	+50.6	33	42	-9	0	8.6	0
Generalized lymphadenopathy....	54	100	100	0	87	49.4	+37.6	43	42	+1	12.9	8.6	+4.3
Positive sputum.....	11	100	100	0	100	49.4	+50.6	45	42	+3	0	8.6	0

liver and spleen had small granulomatous lesions of a similar character. *Histoplasma capsulatum* was isolated from the hilar lymph nodes, but Christie was of the opinion that the child did not die of the infection caused by this organism. The infant also exhibited two discrete lesions in the lower lobes of the lungs, which did show evidence of calcification.

The possibility of subclinical infection with *H. capsulatum* having been assumed for our patients with a strong sensitivity of the skin to histoplasmin (more than 20 mm.), an effort was made to isolate the organism. During the months of June, July and August, 81 patients were selected for special study. These patients all had a sensitivity of the skin indicated by an area of induration and erythema of more than 20 mm. in diameter. Table 5 shows the composition of this group with respect to sensitivity to tuberculin, coccidioidin and histoplasmin. Column 1 indicates the number of patients showing the clinical factors listed in the left margin. Forty persons, or 49.4 per cent, were sensitive to histoplasmin and tuberculin. Thirty-four, or 42 per cent, were sensitive to histoplasmin and coccidioidin. Seven, or 8.6 per cent, were sensitive to histoplasmin only.

A careful search for characteristic bodies in the large mononuclear cells of the bone marrow failed to reveal any *H. capsulatum*. If present in a viable form in this material, the fungus would have been detected with the methods of culture employed. It is possible, however, that an occasional organism would have been missed on microscopic examination. In no instance was *H. capsulatum* isolated from any of the patients in this series.

In addition to the cultures made of the bone marrow of the 81 patients, material from the lymph nodes was cultured for 11 patients showing a progressive exudative pulmonary lesion with negative reaction of the skin to tuberculin. The nodes were divided; one half of the material was fixed for microscopic examination, and the other half was crushed and cultured exactly as was done with the sternal marrow. Again all cultures were sterile, and the microscopic examination revealed only hyperplasia of the lymph nodes. All 11 patients revealed a strongly positive reaction to histoplasmin and a negative reaction to tuberculin in doses of 0.1 mg. of purified protein derivative. However, during the course of six months a sensitivity to tuberculin in the same doses did develop in 4 of the patients. The remaining 7 continued to have a negative reaction even to injections of 0.1 mg. The lesions in the 11 patients were similar in these respects: (1) they were all of the upper lobe; (2) they were exudative; (3) they progressed for two to three months; (4) they regressed for one to two months, and (5) they remained stable for six months.

After six months' observation with no evidence of tuberculous activity, the men were discharged from the hospital. The 4 patients in whom

7 are composed of patients sensitive to tuberculin only, coccidioidin only and histoplasmin only in the order named. With reference to figure 1, it is immediately apparent that 96.6 per cent of a group of 528 patients gave positive reactions to tuberculin (section *A*), while 3.4 per cent gave negative reactions. Fifty-eight and three-fifths per cent were sensitive to histoplasmin (section *B*) and 31.1 per cent were sensitive to coccidioidin (section *C*). Three patients with positive reactions to the coccidioidin and tuberculin tests of the skin were found to have both acid-fast organisms and the spherules of *Coccidioides* in their bronchial secretions simultaneously. In no instance were we able to isolate *H. capsulatum* from the sputum, from lymph nodes or from cultures of the bone marrow in patients with a positive reaction to histoplasmin. Extremely careful mycologic studies were made of all the patients with a sensitivity of the skin to histoplasmin, and it is felt that the presence of viable forms of *H. capsulatum* was ruled out in the tissues examined. While the incidence of sensitivity to one single fungus antigen without concomitant sensitivity to tuberculin was rare, being 1.7 per cent for histoplasmin and 0.6 per cent for coccidioidin, 33.9 per cent of the patients were sensitive to tuberculin only.

In table 2 the patients are divided into three groups. Four hundred and ninety-one, or 93 per cent, were sensitive to tuberculin, 48 per cent were sensitive to histoplasmin and 30 per cent were sensitive to coccidioidin. None of these groups is completely homogeneous, as of the group sensitive to tuberculin 32 per cent were also sensitive to histoplasmin; 6 per cent to coccidioidin and 24 per cent to both histoplasmin and coccidioidin. In the group with sensitivity to histoplasmin, 32.5 per cent were also sensitive to tuberculin and 24.1 per cent to tuberculin and coccidioidin. In the group sensitive to coccidioidin, 6.1 per cent were sensitive to tuberculin and 24.1 per cent to tuberculin and histoplasmin. Certain roentgenologic and physical findings were tabulated as they occurred in each of the three groups. These are shown in table 2. The clinical factors are listed in the left margin, column 1 showing the number of patients exhibiting each. Columns 2, 6 and 10 show the number of patients in each group with these clinical factors. Columns 4, 8 and 12 show the incidence of each factor that would be expected if based on a pure mathematical ratio of each group. The standard deviation of these percentages varied from 1.5 to 3. Columns 5, 9 and 13 show the difference between the observed and the expected occurrence of each of the clinical factors. Column 5 shows that there is no greater occurrence of any of the clinical factors in the group sensitive to tuberculin than would be expected from a computation based on the pure arithmetic ratio of the population of the group. However, less than the expected number of patients with pain in the chest and with

the reaction to tuberculin became positive were discharged on a certificate of disability with the diagnosis of minimal, arrested pulmonary tuberculosis. It is impossible to say whether these 4 patients became infected while in the hospital or whether they were for some unknown reason anergic to tuberculin for the first seven to nine months and later became sensitive for a still unknown reason. For the 7 patients who gave a negative reaction to tuberculin the following type of diagnosis was made: pulmonary fibrosis (lobe involved), cause undetermined, characterized by roentgenologic evidence of parenchymal infiltration (of lobe involved), with normal sputum, negative reactions to the tuberculin cutaneous test and strong sensitivity of the skin to histoplasmin. These patients were sent to duty except in a few instances in which they were discharged from the Service for other reasons.

COMMENT

The problem which initiated this study was one of the differential diagnosis of pulmonary pathema discovered on routine roentgen examination of soldiers being separated from the service. While it is recognized that nontuberculous processes may exist simultaneously in patients with proved tuberculosis, we were not greatly concerned with the patients who presented a typical roentgen picture of tuberculosis and whose sputum contained acid-fast bacilli. Even patients with typical roentgen findings and a positive cutaneous reaction to the tuberculin test in the absence of acid-fast bacilli in the sputum caused little concern in arriving at a presumptive diagnosis, even though we were conscious of the inadequate criteria for such a diagnosis. However, patients with typical roentgen findings and with no sensitivity of the skin to tuberculin were extremely perplexing. Bronchoscopic examinations were made frequently, and a tremendous amount of laboratory work was done for many of them. The behavior of the lesion as observed by serial roentgenograms was frequently of no specific assistance in the etiologic diagnosis. While the battery of skin tests with tuberculin, coccidioidin and histoplasmin was actually of no help in the differential diagnosis, certain interesting observations were made.

The reference to table 1 shows at a glance that the majority of patients gave a weakly positive reaction to all three of the antigens. When the three tests were done simultaneously the patients were observed to fall into one of several sensitivity groups, depending on the combination of sensitivities exhibited at the time. For instance, group 1 is composed of patients who were sensitive to tuberculin, coccidioidin and histoplasmin, group 2 of patients who were sensitive to tuberculin and coccidioidin, group 3 of patients sensitive to tuberculin and histoplasmin and group 4 of patients sensitive to coccidioidin and histoplasmin. Groups 5, 6 and

tabulation and spot map show that there is a fairly even distribution of positive and negative reactors. These include all patients reacting to histoplasmin, including those with a relatively mild degree of sensitivity, characterized by a 5 to 10 mm. area of induration and erythema, as well as those with a severer reaction, characterized by an area of 20 mm. and above. In view of the knowledge of cross sensitivity reactions between histoplasmin, haplosporangin, blastomycin, coccidioidin and probably preparations from several other fungi, this suggests the distribution that one would expect. However, if the distribution of only patients with a relatively strong sensitivity to histoplasmin is studied, the results are those indicated in figure 3 and table 6. In table 6 all patients with a sensitivity to histoplasmin indicated by an area of more than 20 mm.

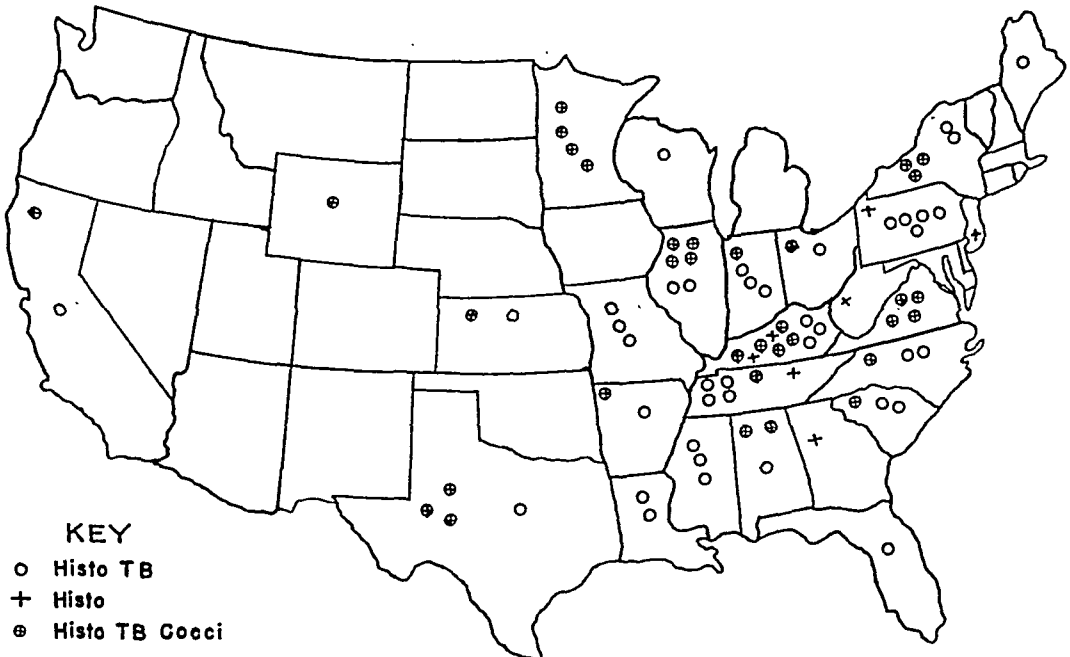


Fig. 3.—Spot map of the United States, showing distribution of 81 patients with strong reactions to histoplasmin (20 mm.) and to tuberculin and coccidioidin.

of erythema and induration are listed. Twelve per cent of the patients from Kentucky and 7 per cent of the patients from Tennessee, Illinois and Pennsylvania exhibited a more or less pronounced sensitivity. In figure 3 the open circles represent patients sensitive to histoplasmin and tuberculin. The plus marks indicate those sensitive to histoplasmin only. The circle inclosing the plus mark indicates sensitivity to histoplasmin, tuberculin and coccidioidin.

Eighty-one patients with a strong reaction to histoplasmin were selected for special study. These patients all reacted with an area of induration and erythema measuring more than 20 mm. The characteristics of the roentgenologic findings and the incidence of splenomegaly, hepatomegaly and generalized lymphadenopathy and of the occurrence of acid-fast organisms in the sputum are given in table 5. The clinical

hepatomegaly were included in his group. In the group sensitive to histoplasmin, there were 12 per cent more than the expected number with hilar calcification and 14.6 per cent more than the expected number with parenchymal calcification. It is interesting to note that 14 per cent more than the expected number had exudative pulmonary lesions in the group sensitive to histoplasmin. In this respect it should be pointed out that 7 patients with a positive reaction to histoplasmin and a negative reaction to tuberculin exhibited an exudative lesion in the upper lobes of the lungs, which progressed for two or three months and then finally regressed and became stationary. These lesions behaved exactly as would have been expected of a minimal tuberculosis lesion in the apexes. However, acid-fast bacilli were never obtained from the sputum of these patients even on bronchoscopic examination and the reaction to the tuberculin test of the skin was negative even with the use of 0.1 mg. of purified protein derivative. In the group sensitive to coccidioidin there was no great difference between the expected and the observed occurrence of any of the clinical factors listed.

Of the 528 patients followed for six months or longer, 167 were found to have pulmonary calcification. Table 3 shows the distribution of these patients with reference to their cutaneous sensitivity. Only 15.3 per cent of the 209 patients who were sensitive to tuberculin had pulmonary calcification. Of these, 5.5 per cent had hilar calcifications and 13.4 per cent had parenchymal calcifications. Of the group sensitive to tuberculin and coccidioidin, 31 per cent showed evidence of pulmonary calcification, and of the group sensitive to tuberculin and histoplasmin, 39 per cent had such evidence. In 13 per cent the calcification was in the hilar region and in 23 per cent in the parenchymal zones. Of the 10 patients with sensitivity to histoplasmin only 7, or 70 per cent, showed pulmonary calcification; in 20 per cent it was in the hilar region and in 50 per cent in the parenchymal zones. Of the 21 patients with negative reactions to all three antigens, 33 per cent showed pulmonary calcification; in 19.3 per cent the calcifications were hilar and in 14.3 per cent parenchymal. These figures are not at all unusual when it is considered that most of the patients sensitive to tuberculin had minimal tuberculosis and that calcification from coccidioidomycosis has been known for some time.⁵ The occurrence of calcified pulmonary lesions in persons sensitive to histoplasmin agrees with the implication made by Palmer, Christie and others that calcified pulmonary lesions are frequently seen in such persons.

About 60 per cent of the 528 patients had sensitivity of the skin to histoplasmin. The distribution of these patients by states is given in table 4 and graphically represented on the spot map in figure 2. The

5. Aronson, J. D.; Saylor, R. M., and Parr, E. I.: Relationship of Coccidioidomycosis to Calcified Pulmonary Nodules, *Arch. Path.* **34**:31-48 (July) 1942.

per cent of the patients with generalized lymphadenopathy also were in this group.

It must be remembered that the presence of pulmonary calcification may be due to a great number of etiologic agents. Roentgenologic evidence of any pulmonary pathema, whether fibrotic, exudative or calcific, calls for the most thorough elicitation of the patient's history and for thorough physical examination as well as for bacteriologic and mycologic studies. However, the sensitivity of the skin to certain antigens such as tuberculin and coccidioidin may at times furnish valuable bits of information to assist in the arrival at the final diagnosis. In the use of the sensitivity of the skin to histoplasmin in the differential diagnosis of pulmonary pathema, one must consider several factors: (1) the known cross sensitivity reactions, (2) the strength of the reaction, (3) the possibility of the existence of a benign infection with *H. capsulatum* and (4) the possibility of a sensitivity reaction secondary to therapy with the antibiotics. One of the patients in this series who originally gave a negative reaction to histoplasmin showed an area of reaction of 10 mm. to a 1 to 1,000 dilution after he had received a course of penicillin for syphilis. The patient had a rather severe urticarial reaction to the penicillin. No explanation for the newly acquired sensitivity to histoplasmin was found.

Histoplasmosis is at present considered to be uniformly fatal; however, cases have been reported³ in which *H. capsulatum* has been recovered from patients in whom histoplasmosis was not the cause of death. It is not known whether these patients would have died ultimately as a result of the infection with *H. capsulatum* or whether the outcome would have been similar to that in the Rhesus monkey infected by Wright and Hachtel in 1941.⁶ This animal was infected with *H. capsulatum* after which several blood cultures which yielded the organism were obtained. When the animal was finally killed, autopsy revealed no evidence of the organism. In DeMonbreun's work, the Rhesus monkeys all died of the infection.⁷ McLeod⁸ reported 2 cases of fatal histoplasmosis in which the reaction to the test with histoplasmin was negative. Christie³ reported a case of fatal histoplasmosis in an infant in whom the reaction to the skin test was positive; the patient's mother and father were also sensitive to histoplasmin.

Evidence so far presented in the literature seems to indicate the possibility of a benign self limiting infection with *H. capsulatum* which

6. Wright, R. B., and Hachtel, F. W.: Histoplasmosis of Darling: Report of a Case, *Ann. Int. Med.* **15**:309-319, 1941.

7. DeMonbreun, W. A.: The Cultivation and Cultural Characteristics of Darling's *Histoplasma Capsulatum*, *Am. J. Trop. Med.* **14**:93-125, 1934.

8. McLeod, J. H.; Emmons, C. W.; Ross, S., and Burke, F. G.: Histoplasmosis, *J. Pediat.* **26**:275-295, 1946.

factors are listed in the left margin. Column 1 shows the number of patients in the group exhibiting each clinical factor listed. The combinations of sensitivity to histoplasmin as related to sensitivity to tuberculin and to coccidioidin are indicated in the top horizontal column. Forty persons were sensitive to histoplasmin and tuberculin, comprising 49.4 per cent of the total of 81. Among them were found 89 per cent of the patients with pulmonary calcification, 90 per cent of those with exudative lesions and 86 per cent of those with fibrotic pulmonary lesions. Also included were 91 per cent of the patients with cavitation as well

TABLE 6.—*Geographic Distribution of Eighty-One Patients with Strong Positive Reactions of the Skin (20 mm. and over) to Histoplasmin Alone and in Combination with Tuberculin and Coccidioidin*

State	Sensitive to Histoplasmin	Sensitive to Histoplasmin, Tuberculin and Coccidioidin	Sensitive to Histoplasmin and Tuberculin	State Total	Percentage of State Total
Wyoming.....	..	1	..	1	1
Tennessee.....	1	1	4	6	7
California.....	..	1	1	2	2
Minnesota.....	..	4	..	4	5
Alabama.....	..	2	1	3	4
Indiana.....	..	1	3	4	5
Virginia.....	..	4	..	4	5
Kentucky.....	2	5	3	10	12
Texas.....	..	3	1	4	5
Arkansas.....	..	1	1	2	2
New York.....	..	3	2	5	6
North Carolina.....	..	1	2	3	4
Illinois.....	..	4	2	6	7
Kansas.....	..	1	1	2	2
South Carolina.....	..	1	2	3	4
Ohio.....	..	1	1	2	2
Florida.....	1	1	1
Pennsylvania.....	1	..	5	6	7
Mississippi.....	3	3	4
Missouri.....	3	3	4
Maine.....	1	1	1
Louisiana.....	2	2	2
Wisconsin.....	1	1	1
West Virginia.....	1	1	1
New Jersey.....	1	1	1
Georgia.....	1	1	1

as all the patients with splenomegaly, hepatomegaly and sputum containing acid-fast organisms. The group of 40 included all patients with a sensitivity to histoplasmin and tuberculin regardless of whether they were sensitive to coccidioidin. In the next group, comprising those sensitive to histoplasmin and coccidioidin, there were 34, or 42 per cent of the total group. These were all patients who were sensitive to histoplasmin and coccidioidin regardless of whether they were sensitive to tuberculin. The group of 7 persons sensitive to histoplasmin only, comprising 8.6 per cent of the total group, included 11.1 per cent of the patients with pulmonary calcification. Ten per cent of those with exudative lesions, 13 per cent of those with fibrotic lesions and 21 per cent of those with lesions of the lower lobes fell in this group. Twelve

3. Efforts to isolate a fungus characteristic of *Histoplasma capsulatum* by microscopic examination and careful mycologic studies of bone marrow, sputum and lymph nodes of the patients with a strong sensitivity of the skin to histoplasmin were consistently nonproductive.

4. Patients with a strong reaction to histoplasmin in a 1 to 1,000 dilution usually showed a mild reaction to coccidioidin in a 1 to 10 dilution; those with a strong reaction to coccidioidin in the 1 to 1,000 dilution usually had a mild reaction to the 1 to 1,000 dilution of histoplasmin. This cross sensitivity reaction is also suggested by the geographic distribution of patients with and without sensitivity to histoplasmin (fig. 2).

5. There was a considerable difference in the geographic distribution of those with strong reactions to histoplasmin as compared to those with mild reactions (with areas of reaction of 5 and 10 mm.) (figs. 2 and 3).

6. The incidence of pulmonary calcifications was greater in the group sensitive to histoplasmin than in the groups sensitive to coccidioidin or tuberculin.

7. Of 528 patients for whom a presumptive diagnosis of pulmonary tuberculosis was made by roentgen studies, 117 were found to have acid-fast bacilli in their bronchial secretions or in gastric washings.

8. The diagnosis of pulmonary tuberculosis was made for 404 patients with only the following evidence of this disease: (a) characteristic roentgen evidence of pulmonary pathema and (b) sensitivity of the skin to tuberculin.

9. For 7 patients with no sensitivity of the skin to tuberculin the diagnosis of pulmonary fibrosis, cause undetermined, was made.

CONCLUSIONS

In the light of the present knowledge of histoplasmosis, the use of the test of sensitivity of the skin to histoplasmin is of limited value in the differential diagnosis of pulmonary disease.

In a group of patients with roentgen evidence of tuberculosis, 93.6 per cent were sensitive to tuberculin, 58.6 per cent were sensitive to histoplasmin and 31.1 per cent were sensitive to coccidioidin. Both histoplasmosis and coccidioidomycosis are known to leave pulmonary pathema similar to that of tuberculosis. Therefore, more exacting criteria for the diagnosis of pulmonary tuberculosis should be available than those of roentgenologic studies and sensitivity of the skin to tuberculin.

The Caulfeild inhibitive test in combination with the tuberculo-complement fixation test or some similar method such as the agglutination test may prove to be essential in the exact diagnosis of minimal tuberculosis in the future.

The present methods used in the differential diagnosis of pulmonary tuberculosis are inadequate.

is associated with complete recovery, a high incidence of pulmonary calcification and a sensitivity of the skin to histoplasmin. Further study with experimental animals will undoubtedly shed some light on this subject.

The presence of a benign type of histoplasmosis is of academic interest but not of great importance to physicians dealing with thoracic diseases. On the basis of the present knowledge of pulmonary disease, the most crying need is for an accurate method of determining the presence of tuberculosis in patients with undiagnosed pulmonary pathema. While a patient may have a sensitivity of the skin to a multitude of antigens, among them histoplasmin, his pulmonary pathema may be the result of an infection with *Paragonimus westermani* or may be some other equally rare condition. A positive reaction to the Mantoux test may have no connection with the abnormal shadow in the roentgenogram under consideration at the moment.

At the present time there is no certainty that the patient with pulmonary disease has tuberculosis unless the tubercle bacilli is demonstrated in the sputum or bronchial secretions or cultured from gastric washings. Even with this evidence, patients with tuberculosis may have additional infections, such as coccidioidomycosis or other fungous diseases or tropical diseases, which must be discovered if scientific therapy is to be instituted.

Ogden and associates⁹ have introduced a method of study employing the tuberculo-complement fixation test in combination with Caulfeild's "inhibitive test" and the Mantoux test, which they claim to be of great diagnostic and prognostic value in the treatment of pulmonary tuberculosis. While Caulfeild's work has been almost universally rejected, it is possible that the addition of some similar method of study will greatly improve our diagnostic acumen in pulmonary disease.

SUMMARY

1. Skin tests with a battery of three antigens—tuberculin, histoplasmin and coccidioidin—were made on 1,220 patients with roentgen evidence of pulmonary pathema compatible with that of pulmonary tuberculosis. Ninety-six and three-fifths per cent were sensitive to tuberculin, 58.6 per cent were sensitive to histoplasmin and 31.1 per cent were sensitive to coccidioidin.

2. Seven patients in the group were strongly sensitive to histoplasmin and gave negative reactions to tuberculin (0.1 mg. of purified protein derivative) and coccidioidin. The lesions in all 7 were similar, with characteristics of tuberculosis, except for the absence of acid-fast bacilli in the bronchial secretions and of sensitivity to tuberculin.

9. Ogden, A., and others: *Foreseeing and Forestalling Tuberculosis*, Dis. of Chest 12:277-329, 1946.

fever, louping ill, Q fever, influenza and coccidioidomycosis, yet in no instance of the infections just mentioned or of the following ones did disease spread farther.

LABORATORY INFECTIONS

Laboratory infections with glanders, poliomyelitis and plague are referred to later in these pages. Rosebury² describes instances of psittacosis, and Haedlicke³ reports 4 cases in which typhoid was contracted by vaccinated persons working with cultures. The disease was described as so mild as to make diagnosis difficult, yet the charts in all 4 cases showed temperatures of 40 C. (104 F.) and the disease lasted from four to seven weeks. Sadusk⁴ observed cases in which typhus was probably contracted by the inhalation of rickettsia-bearing dust in laboratories, and Howe⁵ describes 17 cases of accidentally acquired brucellosis. Sabin himself contracted Rift Valley fever,⁶ and accidental infections have occurred in practically every laboratory in which the disease was studied. Four laboratory workers had Venezuelan equine encephalomyelitis while working with the disease.^{6a}

ANTIBIOTICS

The historic and theoretic aspects of chemotherapy and antibiotic therapy are presented in a series of articles in the *British Medical Bulletin* (40: 4, 1946) and in an essay by Florey.⁷

According to a report,⁸ Chain, one of the developers of penicillin, predicted that synthetic penicillin would never replace the natural product "unless someone invented an entirely new technic unlike anything which now is known in chemistry." Soon afterward, duVigneaud⁹

2. Rosebury, T.; Ellingson, H. V., and Meiklejohn, G.: A Laboratory Infection with Psittacosis Virus Treated with Penicillin and Sulfadiazine, *J. Infect. Dis.* **80**:64-77 (Jan.-Feb.) 1947.

3. Haedlicke, T. A.: Typhoid Fever in Vaccinated Laboratory Workers, *J. Infect. Dis.* **80**:113-116 (Jan.-Feb.) 1947.

4. Sadusk, J. F.: Typhus Fever in the United States Army Following Immunization, *J. A. M. A.* **133**:1192-1199 (April 19) 1947.

5. Howe, C., and others: Acute Brucellosis Among Laboratory Workers, *New England J. Med.* **236**:741-747 (May 15) 1947.

6. Sabin, A. B., and Blumberg, R. W.: Human Infection with Rift Valley Fever Virus and Immunity Twelve Years After Single Attack, *Proc. Soc. Exper. Biol. & Med.* **64**:385-389 (April) 1947.

6a. Koprowski, H., and Cox, H. R.: Human Laboratory Infections with Venezuelan Equine Encephalitis Virus: Report of Four Cases, *New England J. Med.* **236**:647-653 (May 1) 1947.

7. Florey, H. W.: The Use of Micro-Organisms for Therapeutic Purposes, *Yale J. Biol. & Med.* **79**:101-117 (Oct.) 1946.

8. The Merck Report, October 1946.

9. du Vigneaud, V.; Carpenter, F. H.; Holley, R. W.; Livermore, A. H., and Rachele, J. R.: Synthetic Penicillin, *Science* **104**:431-433 (Nov. 8) 1946.

Progress in Internal Medicine

INFECTIOUS DISEASES

Thirteenth Annual Review of Significant Publications

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PHILADELPHIA

Papers published during the past year dealing with infectious diseases contain no spectacular report such as readers have become accustomed to expect in recent times. Except for encouraging effects of streptomycin in tuberculosis, the synthesis of penicillin, information that under certain conditions both penicillin and streptomycin actually stimulate bacterial growth and the inhibiting effect of certain other antibiotics on neoplastic cells, studies in the field of antibiotics have been in the nature of odds and ends. The sulfonamide compounds are found to be of less and less use and are obsolete for many conditions. Interest in viral hepatitis and viral pneumonia has waned apparently in proportion to the decrease in the incidence of these infections consistent with the natural rise and fall of epidemic diseases. A new rickettsial disease was discovered in New York city.

The feasibility of biologic warfare based on facts and theory at hand up to 1942 was discussed in an eighty page paper.¹ One wonders if so long a paper is justified if much or all of the pertinent information gleaned in intensive study since 1942 is withheld. Reading it leaves a feeling that the chances of success in causing serious human epidemics are poor unless, of course, they are started in regions devastated by natural or artificial catastrophies in which natural and technical defensive measures are inoperative. It is comforting to recall that the concatenation of numerous known and unknown factors essential to cause an epidemic is a fortuitous one which it is almost impossible to achieve deliberately. About thirty diseases of human beings are listed as possible offensive weapons. Among them is bacillary dysentery, but elsewhere in the present review the difficulty of causing dysentery even in volunteers who drank heavy inoculums of bacilli is cited. Because air-borne infections frequently cause accidental infection among laboratory workers who handle the causative agents or are exposed to them, these also have been considered. Among them are tularemia, yellow

From the Jefferson Medical College and Hospital.

1. Rosebury, T.; Kabat, E. A., and Boldt, M. H.: *Bacterial Warfare: A Critical Analysis of the Available Agents, Their Possible Military Application, and the Means for Protection Against Them*, J. Immunol. **56**:7-96 (May) 1947.

biotic agents increase the growth rate of certain strains of staphylococci and streptococci, and because of this, they emphasize the danger of using antibiotics therapeutically in subeffective dosage. In other studies,¹² exposure of strains of *Hemophilus influenzae* to penicillin gave rise to the appearance of pleuropneumonia-like bacilli.

Although most physicians favor the intrathecal injection of penicillin in addition to intramuscular injection for meningitis, I have felt that the latter is sufficient. Now comes report¹³ of spinal arachnoiditis, transverse myelitis and injury to the brain after intraspinal injection. The authors recommend early parenteral injection of maximum doses of penicillin as preferable to intraspinal injection.

In two papers¹⁴ published in abstract, report is made of the effect of caronamide (4'-carboxyphenylmethanesulfonanilide) given orally on the amount of penicillin in the blood. The substance delays the excretion of penicillin by the renal tubules and thereby increases the amount retained in the blood from two to seven times. It seems questionable whether such a procedure is worth the risk of possible harm when levels in the blood attained with the usual doses are adequate for most purposes. More detailed studies are published elsewhere.^{14a}

Streptomycin.—Older information on the subject is reviewed adequately elsewhere.¹⁵

Intensive studies on the effect of streptomycin on tuberculosis are in progress. Reports are favorable to the extent that streptomycin appears to suppress tuberculous infection rather than to eradicate it. The drug is bacteriostatic and not bactericidal in the amounts in which it reaches the tissues. Treatment requires large dosage over long periods and is subject to toxic side effects. As an indication of the great interest in the matter, the use of streptomycin for tuberculosis is discussed in abstract form by six groups of investigators in the program of the 1947 meetings of the American Society for Clinical Investigation. All report strikingly favorable effects. There was

12. Dienes, L.: Isolation of Pleuropneumonia-like Organisms from *H. Influenzae* with the Aid of Penicillin, *Proc. Soc. Exper. Biol. & Med.* **64**:166-168 (Feb.) 1947.

13. Erickson, T. C.; Masten, M. G., and Suckle, H. M.: Complication of Intrathecal Use of Penicillin, *J. A. M. A.* **132**:561-565 (Nov. 9) 1946.

14. Boger, W. P., and others: High Penicillin Plasma Concentration by the Use of Caronamide, a Compound that Inhibits Penicillin Excretion by the Renal Tubules, paper read before the American Society for Clinical Investigation, May 5, 1947. Parker, R. F., and Albright, R.: The Effect of Caronamide in Inhibiting Penicillin Excretion, *ibid.*

14a. Crosson, J. W., and others: Caronamide for Increasing Penicillin Plasma Concentration in Man, *J. A. M. A.* **134**:1528-1532 (Aug. 30) 1947.

15. Murray, R.; Paine, T. F., and Finland, M.: Streptomycin, *New England J. Med.* **236**:701-712 (May 8); 748-760 (May 15) 1947.

announced the synthesis of penicillin. There is no indication at present, however, that this accomplishment will allow production of synthetic penicillin on a commercial basis, but the way is opened for the possible development of new compounds which may even exceed penicillin in therapeutic value.

In a series of papers in the February issue of the *Journal of Experimental Medicine* Eagle writes that penicillin F, G, K and X are all inactivated to some degree by serum by two distinct mechanisms. In the slow inactivation penicillin X was least affected. By the more important rapid factor penicillin K alone was inactivated, especially when it was present in small amounts. The highest sustained amount in the blood was afforded by penicillin X and the lowest by K. Furthermore, although efforts now are made commercially to obtain a high proportion of penicillin G in the products used for treatment, penicillin X is twice as effective as penicillin G against pneumococci, streptococci and gonococci. These facts, in addition to its slower inactivation by serum, would seem to make penicillin X the one of choice.

Others^{9a} interpret the differences in the amount of penicillin fractions in the blood on the basis of their difference in degree of binding with proteins of the serum. Evidence is given to show that the previous findings of larger and more prolonged amounts of penicillin X in the blood and the lower amounts and rapid disappearance of penicillin K were artefacts caused by the action of serum during the process of assaying. Therefore, differences in the therapeutic effectiveness of the various fractions of penicillin cannot be explained by the differences in the amount and duration as measured in the blood.

Penicillin rapidly deteriorates when mixed with glycerin, propylene glycol and other viscous agents. Stability also varies with the particular salt used in the preparation.¹⁰

Important observations indicate that in low concentration both penicillin and streptomycin, like certain drug and chemical agents, serve as stimulants to bacterial growth^{10a} but in large amounts they are deterrents. Curran and Evans¹¹ show how small amounts of anti-

9a. Tompsett, R.; Shultz, S., and McDermott, W.: Influence of Protein-Binding on the Interpretation of Penicillin Activity in Vivo, *Proc. Soc. Exper. Biol. & Med.* **65**:163-172 (June) 1947.

10. Ferlauto, R. J., and Clymer, H. A.: Stability of Penicillin in Glycerin and Glycols, *Science* **105**:130-131 (Jan. 31) 1947.

10a. Acquired Resistance to Penicillin, Annotation, *Brit. M. J.* **2**:101-102 (July 19) 1947.

11. Curran, H. R., and Evans, F. R.: Stimulation of Sporogenic and Non-sporogenic Bacteria by Traces of Penicillin or Streptomycin, *Proc. Soc. Exper. Biol. & Med.* **64**:231-233 (Feb.) 1947.

should be used in therapy. In Logan and Herrell's²⁰ experience with these three agents, improvement in 2 patients did not occur until streptomycin was used. Streptomycin alone is curative in mild or moderately severe attacks. In most reports of the treatment of this heretofore almost invariably fatal disease, the mortality rate has been greatly diminished by the use of streptomycin.

Streptomycin was used with success in the treatment of 11 patients with tularemic pneumonia²¹ and in pneumonic plague. It was also of value in 8 cases of bacillary dysentery when given orally and parenterally in doses of 1 to 4 Gm. daily for three to sixteen days.²² Four patients with gonorrheal urethritis were successfully treated with 0.1 Gm. of streptomycin at hourly intervals for five doses.^{22a}

A review of the literature concerning infections caused by *Bacillus pyocyaneus* and studies of the effect of streptomycin on them has been presented.²³ According to the author, this infection is becoming more common because of the suppression of other competitively invasive bacteria by chemical and antibiotic agents. Harris and others²⁴ obtained good results in 50 per cent of patients with infection of the urinary tract, especially when the urine was kept alkaline. Finland's group²⁵ report good results in only 4 of 12 cases. The failures were apparently due to the development of resistance to streptomycin on the part of the causative bacteria.

Certain patients with pneumonia caused by *H. influenzae* or by Friedländer's bacilli were greatly benefited by streptomycin, and others were not.²⁶ Resistance against streptomycin developed by the causative bacteria appears to be a factor in poor therapeutic results in some cases.

20. Logan, G. B., and Herrell, W. E.: Streptomycin in the Treatment of Influenzal Meningitis of Children, Proc. Staff Meet., Mayo Clin. **21**:393-400 (Oct. 16) 1946.

21. Hunt, J. S.: Pleuropulmonary Tularemia: Observations on Twelve Cases Treated with Streptomycin, Ann. Int. Med. **26**:263-276 (Feb.) 1947.

22. Pulaski, E. J., and Anspacher, W. H.: Streptomycin in Intestinal Infections, Bull. U. S. Army M. Dept. **6**:750-760 (Dec.) 1946.

22a. Chinn, B. D., and others: Treatment of Gonorrhea with Streptomycin, Am. J. Syph., Gonorr. & Ven. Dis. **31**:268-270 (May) 1947.

23. Stanley, M. M.: *Bacillus Pyocyaneus* Infections: A Review; Report of Cases and Discussion of New Therapy Including Streptomycin, Am. J. Med. **2**:253-277 (March); 347-367 (April) 1947.

24. Harris, H. W., and others: Streptomycin Treatment of Urinary Tract Infections, with Special Reference to the Use of Alkali, Am. J. Med. **2**:229-250 (March) 1947.

25. Finland, M., and others: Development of Streptomycin Resistance During Treatment, J. A. M. A. **132**:16-21 (Sept. 7) 1946.

26. Harris, H. W.; Murray, R.; Paine, T. F., and Finland, M.: Streptomycin Treatment of Pulmonary Infections: Clinical and Bacteriologic Studies of Six Cases, New England J. Med. **236**:611-622 (April 24) 1947.

prompt disappearance of ulcerative lesions of the trachea and bronchi but only temporary symptomatic improvement of other lesions in the lungs. Draining tuberculous sinuses healed with one to twenty weeks of therapy. In Bunn's report of 6 patients with miliary or meningeal tuberculosis, 4 were apparently cured. Complete clearing of the miliary lesions occurred roentgenographically. The dosage varied from 1.2 to 4 Gm. daily often for as long as one hundred and twenty days. D'Esopo's group noted resolution "to a greater or lesser extent" in 77 per cent of 120 patients with far advanced pulmonary tuberculosis treated for four months. No new lesions developed during the course of treatment, nor did lesions progress. Therapy is most effective for exudative lesions and is suppressive rather than definitive. In the program and elsewhere¹⁶ Hinshaw and Feldman added further favorable evidence to their previous data and concluded that the permanence of the good results depends on how much natural healing occurs before the tubercle bacilli become resistant to streptomycin. In the experience of McDermott and his co-workers, therapy was continued in some patients for three hundred days. Resistance of the bacilli to streptomycin developed after the fourth week in most cases, and relapse often occurred when that took place. Toxic effects from streptomycin usually accompanied prolonged therapy.

Some observers¹⁷ are pessimistic about the curative effects of streptomycin, since in clinical tuberculosis the bacilli appear to reproduce at long irregular periods undeterminable by any means and it is possible to provide an adequate amount of the drug in the tissues for only brief periods. Furthermore, there is no evidence that streptomycin enters important organs in appreciable amounts over long periods. The clinical value of streptomycin in tuberculosis, they feel, is limited.

Streptomycin together with type-specific antiserum and sulfadiazine is recommended for the treatment of meningitis caused by *H. influenzae*¹⁸ for the following reason.¹⁹ Cultures of *H. influenzae* almost always contain small numbers of bacilli which are probably variant forms and are highly resistant to streptomycin. All sensitive bacilli are eliminated by growth in medium containing streptomycin, but since the remaining resistant ones are sensitive to sulfadiazine both agents

16. Hinshaw, H. C.; Feldman, W. H., and Pfuetze, K. H.: The Treatment of Tuberculosis with Streptomycin: A Summary of Observations on One Hundred Cases, *J. A. M. A.* **132**:778-782 (Nov. 30) 1946; Streptomycin in Treatment of Clinical Tuberculosis, *Am. Rev. Tuberc.* **54**:191-203 (Sept.) 1946.

17. Corper, H. J., and Cohn, M. L.: The Tubercle Bacillus and Fundamental Chemotherapeutic and Antibiotic Action, *Yale J. Biol. & Med.* **19**:1-22 (Oct.) 1946.

18. Alexander, H. E.: Streptomycin in Pediatrics, *J. Pediat.* **29**:192-202 (Aug.) 1946.

19. Alexander, H. E., and Lindy, G.: Mode of Action of Streptomycin on Type b *Hemophilus Influenzae*, *J. Exper. Med.* **85**:607-621 (June) 1947.

A combination of the two agents is more effective, as stated by Smadel at the Surgeon General's symposium in Washington, May 5, 1947.

Weinstein^{32a} points out the danger of upsetting the balance of different pathogenic bacteria normally present in the body by the use of penicillin or streptomycin. Either agent may cure the primary disease by suppressing bacteria sensitive to their effects but may permit other resistant bacteria to multiply and become invasive, causing a new disease. Such infections may arise from bacteria already present but also from those introduced during the therapeutic procedure. Cases are reported in which infections with resistant *H. influenzae*, *Klebsiella pneumoniae* and staphylococci all caused serious disease in patients treated with penicillin or streptomycin for other infections.

The combined use of penicillin and streptomycin is condemned because of the occurrences just mentioned and of the possibility of sensitizing patients needlessly against either antibiotic. The use of antibiotic therapy has increased rather than decreased the need for accurate and repeated bacteriologic diagnosis in the control of infectious diseases.

Other Antibiotics.—Meleney reports³³ further favorable results from local therapy of surgical infections with bacitracin, an antibiotic agent made by a gram-positive bacillus isolated from a patient named Tracey. The substance affects most of the bacteria sensitive to penicillin and some which are resistant to penicillin. It will be of importance only if it succeeds when other therapy fails.

A related antibiotic, subtilin, has a powerful therapeutic action against experimental infection with hemolytic streptococci in mice and against anthrax in guinea pigs.³⁴ Filtrates from cultures of certain molds, especially of *Aspergillus terreus*, inhibited the growth of *Brucella abortus* in high dilution.³⁵ Another antibiotic agent derived from California Spanish moss, a lichen (*Ramalina reticulata*), when given subcutaneously retards the progress of tuberculosis in guinea pigs infected with human tubercle bacilli.³⁶ In another study, glycerite of

32a. Weinstein, L.: The Spontaneous Occurrence of New Bacterial Infections During the Course of Treatment with Streptomycin and Penicillin, *Am. J. M. Sc.* **214**:56-63 (July) 1947.

33. Meleney, F. L., and Johnson, B.: Bacitracin Therapy: The First Hundred Cases of Surgical Infections Treated Locally with the Antibiotic, *J. A. M. A.* **133**:675-680 (March 8) 1947.

34. Salle, A. J., and Jann, G. J.: Subtilin-Antibiotic Produced by *Bacillus Subtilis*: V. Effect on *Streptococcus Pyogenes* Infections in Mice, *Proc. Soc. Exper. Biol. & Med.* **63**:519-520 (Dec.) 1946; IV. Effect of Subtilin on the Course of Experimental Anthrax Infection in Guinea Pigs, *ibid.* **63**:41-42 (Oct.) 1946.

35. Beal, G. A.: Antibiotic Activity of Certain Molds Against *Brucella*, *Proc. Soc. Exper. Biol. & Med.* **64**:118-120 (Jan.) 1947.

36. Marshak, A.: A Crystalline Antibacterial Substance from the Lichen *Ramalina Reticulata*, *Pub. Health Rep.* **62**:3-19 (Jan. 3) 1947.

Twenty-three patients²⁷ with lymphogranuloma inguinale were benefited by daily doses of 0.3 to 1 Gm. of streptomycin and total dosages of 3.3 to 4.6 Gm. given over six to forty-five days, but relapses occurred. The authors regard streptomycin as the most effective remedy for the disease.

The reason for the failure of streptomycin to cure brucellosis caused by strains of *Brucella* highly sensitive to the drug in culture medium is unknown. Resistance to streptomycin, which develops in some but not in all strains of *Brucella* is not the only cause,²⁸ nor is the intracellular location of brucellas and of typhoid bacilli a tenable explanation of poor therapeutic results since *Pasteurella tularensis* is also present intracellularly yet the infection is controlled by streptomycin. The existence and persistence of streptomycin-resistant variant forms, as in the case of *H. influenzae*, dysentery bacilli²⁹ and meningococci,³⁰ offer a better explanation for therapeutic failure at present. It seems that variant or mutant forms resistant to streptomycin are constantly present in bacterial populations. Since many of these are virulent, they continue to grow and cause disease in the presence of the antibiotic, while the other drug-sensitive ones are suppressed.

A surprising discovery was reported by Miller and Bohnhoff³⁰ similar to that of Curran and Evans mentioned on a previous page. Certain variant forms of meningococci actually need streptomycin for growth. They were virulent for mice only in the presence of streptomycin. A strain of *Staphylococcus* was rendered resistant to three antibiotic preparations—after twelve transfers in medium containing streptomycin, after twenty-five transfers with streptothricin and after thirty-two with penicillin.³¹ The resistance to one antibiotic did not result in increased resistance to the others.

Streptomycin has a slight inhibiting effect on typhus rickettsias grown in eggs, but paraaminobenzoic acid was much more suppressive.³²

27. Greenblatt, R. B., and others: Streptomycin in the Therapy of Granuloma Inguinale, *Proc. Soc. Exper. Biol. & Med.* **64**:389-390 (April) 1947.

28. Hall, W. H., and Spink, W. W.: In Vitro Sensitivity of *Brucella* to Streptomycin: Development of Resistance During Streptomycin Treatment, *Proc. Soc. Exper. Biol. & Med.* **64**:403-406 (April) 1947.

29. Klein, M., and Kimmelman, L. J.: The Role of Spontaneous Variants in the Acquisition of Streptomycin Resistance by the Shigellae, *J. Bact.* **52**:471-479 (Oct.) 1946.

30. Miller, C. P., and Bohnhoff, M.: Development of Streptomycin-Resistant Variants of Meningococci, *Science* **105**:620-621 (June 13) 1947.

31. Sullivan, M.; Stahly, G. L., and Birkeland, J. M.: Reciprocal Sensitivities of *Staphylococcus Aureus* to Streptomycin, Streptothricin and Penicillin, *Science* **104**:397-398 (Oct. 25) 1946.

32. Morgan, H. R.; Stevens, D. A., and Snyder, J. C.: Effect of Streptomycin on Growth of Rickettsiae in Eggs, *Proc. Soc. Exper. Biol. & Med.* **64**:342-345 (March) 1947.

Economo's lethargic type, as seen in 1918, and others had myelitis or polyneuritis. It was uncertain if the virus of influenza B was the cause or if another neurotropic virus was a secondary invader. With the knowledge that influenza viruses at times are neurotropic, there is reason to believe that influenza B virus was responsible.

Influenza Vaccine.—There is no doubt that influenza vaccines have prophylactic value against infection with homologous strains of influenza viruses. In Hirst's study⁴³ there were only 3 cases of influenza among 550 students vaccinated with a mixture of A and B influenza vaccine, as compared with 132 cases among 1,050 unvaccinated students, representing attack rates of about 0.5 and 12.5 per cent respectively.

In spite of the advantages of vaccine as exhibited in such carefully controlled studies, one wonders if vaccine as it is now prepared will be of practical value for general use under ordinary conditions against so mild a disease. There are at present at least four disadvantages, as follows:

A. Immunity conferred by actual disease is short, and immunity conferred by vaccine is even less complete and durable, as a rule lasting no longer than several months. Therefore, in any given season revaccination at intervals is needed. Furthermore, since epidemics are unpredictable the efforts and expense of vaccination are wasted if no epidemic appears. A dose of vaccine costs about one dollar.

B. Vaccines as now made are strain specific, and significant immunologic differences are known to exist even among strains of A virus. In Sugg's experiments,⁴⁴ animals infected with one A type virus were susceptible to reinfection with a different A type virus within four to ten weeks. In reports by Henlé, Francis^{44a} and Smadel^{44b} and their co-workers, epidemics caused by a type A strain which differed immunologically from the strain used in the vaccine broke out shortly after vaccination. One wonders how many other different A or B strains may exist to cause similar failures.^{44c}

43. Hirst, G. K.; Vilches, A.; Rogers, O., and Robbins, C. L.: The Effect of Vaccination on the Incidence of Influenza B, *Am. J. Hyg.* **45**:96-106 (Jan.) 1947.

44. Sugg, J. Y., and Magill, T. P.: Significance of Antigenic Differences Among Strains of Influenza A Virus in Reinfection of Ferrets, *Proc. Soc. Exper. Biol. & Med.* **63**:1-5 (Oct.) 1946.

44a. Francis, T.; Salk, J. E., and Quilligan, J. J.: Experience with Vaccination Against Influenza in the Spring of 1947, *Am. J. Pub. Health* **37**:1013-1016 (Aug.) 1947.

44b. Smadel, J. E.: Research in Virus Diseases, *Bull. U. S. Army M. Dept.* **7**:795-808 (Sept.) 1947.

44c. Francis, T.: Apparent Serological Variation Within a Strain of Influenza Virus, *Proc. Soc. Exper. Biol. & Med.* **65**:143-147 (June) 1947.

hydrogen peroxide applied as a wet dressing apparently favored the healing of long-standing tuberculous diseases.³⁷ Kidd³⁸ reports the suppressive effect of two antibiotic agents on tumor cells in cultural experiments.

INFECTIONS OF THE RESPIRATORY TRACT

If, as stated in textbooks, pandemics of influenza happen every thirty years, one is due next year. However, pandemics have been predicted repeatedly during the upheavals and hardships incident to the war, but none has come. Another pandemic of the magnitude of those of 1889 and 1918 probably will never recur unless some cataclysmic event disrupts the world or unless a new variant or mutant form of influenza virus becomes rampant. It is believed that the greatly increased intermingling of persons by extensive traveling has distributed various current influenza viruses and infections therewith so widely as to develop widespread partial immunity. Furthermore, in the event of a pandemic, the availability of specific therapeutic agents no doubt would greatly decrease the mortality rate from secondary pyogenic bacterial pulmonary infections.

Small epidemics of influenza B were reported from England³⁹ and the West Indies⁴⁰ synchronous with other outbreaks elsewhere in the world in 1945 and 1946. The strain varied somewhat from the standard Lee strain of B virus disease. Clinically, the disease was indistinguishable from influenza A. In Jackson's group⁴⁰ pneumonia occurred in 14 per cent of patients and was presumably caused by pneumococci. In influenza B observed in Rochester, N. Y., no benefit was noted from the prophylactic use of sulfadiazine.⁴¹ Rales were heard in 4 of 46 cases, and the bronchial markings were intensified in 17 of 23 patients studied roentgenographically, indicating the frequency with which the lungs are involved. During another outbreak of influenza B, Leigh⁴² studied a group of patients with neurologic disturbances presumably caused by the virus. Some had encephalitis resembling von

37. Brown, E. A., and Slanetz, L. W.: Antiseptic Action of Glycerite of Hydrogen Peroxide on Mycobacterium Tuberculosis (var. Hominis), *Science* **105**:312-313 (March 21) 1947.

38. Kidd, J. G.: Effects of an Antibiotic from *Aspergillus Fumigatus* Fresenius on Tumor Cells in Vitro, and Its Possible Identity with Gliotoxin, *Science* **105**:511-513 (May 16) 1947.

39. Dudgeon, J. A., and others: Influenza B in 1945-46, *Lancet* **2**:627-631 (Nov. 2) 1946.

40. Jackson, W. P. V.: Influenza B Among West Indians: Outbreaks in the Bahamas and in England, *Lancet* **2**:631-635 (Nov. 2) 1946.

41. Bruce, R. A., and Slavin, H. B.: A Study of an Outbreak of Influenza B in Rochester, N. Y., *Am. J. M. Sc.* **213**:129-134 (Feb.) 1947.

42. Leigh, A. D.: Infections of the Nervous System Occurring During an Epidemic of Influenza B, *Lancet* **2**:936-938 (Dec. 21) 1946.

Influenza virus particles contain ribonucleic and desoxyribonucleic acids and carbohydrate-rich fractions of mannose, galactose and glucosamine units.⁵⁰

Other Acute Diseases of the Respiratory Tract.—Modern knowledge of the minor ailments was reviewed by Reimann.⁵¹ On clinical grounds, despite similarities several entities stand out, grouped as the common cold, nonbacterial pharyngitis, grip, febrile catarrh, viroid and influenza. In each of these real and supposed entities pneumonia occurs in a considerable number of patients, raising the question of whether it is caused by the same agent and is a severe form of the disease or by secondary bacterial invaders as a complication. The measures used for prevention and treatment are critically reviewed, and an outline of rational management is given.

In discussing one of the entities, nonbacterial exudative pharyngitis, members of the Commission on Acute Respiratory Diseases published information⁵² which has already appeared in their other papers, namely, that a form of sore throat not caused by hemolytic streptococci commonly occurs. It can be differentiated from the streptococcic forms by its milder clinical characteristics, the absence of streptococci on repeated cultures and the absence of serologic evidence of infection therewith. In subsequent studies^{52a} another mild infection called ARD (acute respiratory disease) was described and shown to be immunologically different from the common cold and from viral pneumonia. The infection is characterized by mild sore throat, but no mention is made as to whether or not it is the same as the exudative pharyngitis described by the same investigators.

In contrast with this form of pharyngitis, Rantz and his associates⁵³ studied an outbreak of hemolytic streptococcic sore throat. Clinical diagnosis was correct in 70 per cent of cases. The throat was painful,

50. Knight, C. A.: The Nucleic Acid and Carbohydrate of Influenza Virus, *J. Exper. Med.* **85**:99-115 (Jan.) 1947.

51. Reimann, H. A.: Viral Infections of the Respiratory Tract: Their Treatment and Prevention, *J. A. M. A.* **132**:487-493 (Nov. 2) 1946.

52. Exudative Tonsillitis and Pharyngitis of Unknown Cause, Commission on Respiratory Diseases, *J. A. M. A.* **133**:588-593 (March 1) 1947.

52a. The Commission on Acute Respiratory Diseases: Experimental Transmission of Minor Respiratory Illness to Human Volunteers by Filter-Passing Agents: I. Demonstration of Two Types of Illness Characterized by Long and Short Incubation Periods and Different Clinical Features, *J. Clin. Investigation* **26**:957-973 (Sept.) 1947; II. Immunity on Reinoculation with Agents from the Two Types of Minor Respiratory Illness and from Primary Atypical Pneumonia, *ibid.* **36**:974-982 (Sept.) 1947.

53. Rantz, L. A.; Boisvert, P. J., and Spink, W. W.: Hemolytic Streptococcic and Nonstreptococcic Diseases of Respiratory Tract: Comparative Clinical Study, *Arch. Int. Med.* **78**:369-386 (Oct.) 1946.

C. According to Salk and Francis⁴⁵ influenza vaccine causes local and systemic reactions similar to those occurring after antityphoid vaccination. In many cases the discomfort caused is greater than that from influenza itself.

D. Vaccine is now prepared in eggs, and since about 10 per cent of persons are allergic in general and 10 per cent of these are allergic to egg protein, it becomes necessary to exert caution when using vaccine to avoid serious and even fatal reactions.⁴⁶ Before injections of vaccine of this type, all recipients should be questioned for sensitivity or tested intradermally before each injection. This measure increases the labor and expense of mass vaccination but safely eliminates the small percentage (0.5 per cent) of persons in whom dangerous reaction may occur. Vaccines should be as free from egg protein as possible. Curphy reports⁴⁷ a fatal allergic reaction in a child of 3 vaccinated with A and B vaccine, caused either by the egg protein component or by the virus itself.

Burnet and his associates⁴⁸ discuss a "receptor gradient" in erythrocytes for the group of viruses causing mumps and influenza. Enzymes made by certain bacteria remove virus receptors by changing the surface character of the red cells so that they become less sensitive to clumping by viruses. Two theoretic implications arise: one, that enzymes play a role in the initial invasion of cells by viruses; the other, that the enzymatic effect may open the way to a new therapeutic approach.

In another study⁴⁹ Burnet and Anderson show how the virus of Newcastle disease of chickens clumps human erythrocytes as influenza virus does. Cells treated with the virus of the Newcastle disease develop a new antigenic character which makes them agglutinable with either Newcastle disease immune serum or serum from patients who had infectious mononucleosis. These effects suggest a new approach to the study of infectious mononucleosis.

45. Salk, J. E., and Francis, T.: Immunization Against Influenza, *Ann. Int. Med.* **25**:443-452 (Sept.) 1946.

46. Ratner, B., and Untracht, S.: Allergy to Virus and Rickettsial Vaccines: I. Allergy to Influenza A and B Vaccine in Children, *J. A. M. A.* **132**:899-905 (Dec. 14) 1946.

47. Curphy, T. J.: Fatal Allergic Reaction Due to Influenza Vaccine, *J. A. M. A.* **133**:1062-1064 (April 12) 1947.

48. Burnet, F. M.; McCrae, J. F., and Stone, J. D.: Modification of Human Red Cells by Virus Action: I. Receptor Gradient for Virus Action in Human Red Cells, *Brit. J. Exper. Path.* **27**:228-235 (Aug.) 1946.

49. Burnet, F. M., and Anderson, S. G.: II. Agglutination of Modified Human Red Cells by Serum from Cases of Infectious Mononucleosis, *Brit. J. Exper. Path.* **27**:236-243 (Aug.) 1946.

pandemic proportions in the years 1942 to 1944 to a few sporadic cases during the past winter consistent with the natural waxing and waning of epidemic diseases. In my experience it was outnumbered by cases of pneumococcic pneumonia, as in former years.

Adamson and Beamish,⁵⁹ in agreement with my own view, state that the term "atypical pneumonia" has resulted in much confusion in nomenclature of disease of the respiratory tract. They prefer to apply the term pneumonia only to pneumococcic pneumonia, other forms to be called pneumonitis. The term pneumonitis, they write, is a clinically descriptive one and should be used for these conditions: (1) common cold pneumonitis, (2) influenzal pneumonitis, (3) contamination pneumonitis, (4) exacerbation pneumonitis, (5) atelectatic pneumonitis, (6) allergic pneumonitis, (7) pneumonitis due to known viruses and rickettsias and (8) pneumonitis due to unknown viruses.

Eaton and his associates,⁶⁰ pursuing their previous lead, found increases of antibody titer for Eaton's AP (atypical pneumonia) virus in 62 per cent of 84 cases of viral pneumonia and in 19 per cent of 77 cases of undifferentiated infections of the respiratory tract without pneumonia. In only 35 per cent of patients with pneumonia and in only 2 per cent of those without pneumonia was agglutinin for streptococcus MG present. These results, according to the authors, aid in delineating another disease of the respiratory tract as an etiologic entity in line with influenza, both of which may occur in sporadic or epidemic form with or without pneumonia.

A surprising number of instances of pneumonia, clinically unsuspected and unrecognized, are brought to light by roentgenography in apparently normal persons. Stuart,⁶¹ who studied 19,000 recruits, found evidence of "atypical pneumonia" in 42, or 0.2 per cent, each of whom were ambulant but had "colds."

56. Sargent, F.; Lombard, O. M., and Sargent, V. W.: Further Studies on the Resistance to the Common Cold: The Importance of Constitution, *Am. J. Hyg.* **45**:29-32 (Jan.) 1947.

57. Ziegler, J. E., and others: Diagnosis of Acute Respiratory Tract Infections, *Am. J. M. Sc.* **213**:268-281 (March) 1947.

58. Reimann, H. A.: Viral Pneumonias and Pneumonias of Probable Viral Origin, *Medicine* **26**:167-219 (May) 1947.

59. Adamson, J. D., and Beamish, R. E.: Clinical Differentiation in the Syndrome Called Atypical Pneumonia, *Canad. M. A. J.* **56**:361-365 (April) 1947.

60. Eaton, M. D., and Van Herick, W.: Serological and Epidemiological Studies on Primary Atypical Pneumonia and Related Acute Upper Respiratory Disease, *Am. J. Hyg.* **45**:82-95 (Jan.) 1947.

61. Stuart, F. G.: Pathological Manifestations and Anatomical Variations in Pre-Enlistment Chest Roentgenograms, *Canad. M. A. J.* **52**:477-481 (May) 1945.

edematous and inflamed, with an exudate and swollen regional lymph nodes, as compared with nonstreptococcic infections in which the nasopharyngeal mucous membrane was nearly normal. However, according to observations made by the Army group and by my own group, inflammation, edema and exudate are present in both conditions but are less severe in the nonbacterial forms. Variations in severity of both forms make diagnosis in the individual case unreliable without cultural and serologic proof. No reference is made by either group to Adam's study,⁵⁴ in which the exudate in nonbacterial pharyngitis is composed chiefly of mononuclear cells in contrast with a polymorphonuclear exudate in streptococcic infection. The cellular reaction is of aid in diagnosis. Gannet and Deutsch in previous work found no immunity to colds after prophylactic injection of a dose of gamma globulin. In student volunteers given monthly injections of gamma globulin, Adams and Smith⁵⁵ seemed to show that infections of the respiratory tract occurred less often than in an equal-sized control group. No accidental serum hepatitis was observed.

According to a study by Sargent and his aides,⁵⁶ there appears to be an undefined constitutional or genetic factor which is operative in the etiology of the common cold.

Diagnosis.—In a paper pointing out clinical differential diagnostic difficulties in the group of infections of the respiratory tract encountered during epidemics of influenza Ziegler and his associates⁵⁷ depend more on laboratory tests for diagnosis. In a series of 26 patients some admitted as having viral pneumonia proved to have pneumococcic pneumonia and others had influenza. Because certain patients with influenza had pneumonia, they suspected the presence of two concurrent infections, influenza and viral pneumonia. It would seem more reasonable, however, to assume that the influenza virus alone caused the pneumonia. The authors rely heavily on the tests for agglutinin for streptococcus MG and for cold agglutination in the diagnosis of viral pneumonia, yet these reactions occur late in the disease in only half of the cases. In diagnosis, dependence should not be placed on the therapeutic response to sulfonamide drugs or penicillin.

Viral Pneumonias.—Besides a comprehensive review of the subject of viral pneumonia,⁵⁸ few papers have appeared during the year. Viral pneumonia, as now recognized, has apparently declined from almost

54. Adams, J. M.; Pennoyer, M. M., and Whiting, A. M.: Pathologic Study of the Acutely Inflamed Human Pharynx in Influenza Infection, *Am. J. Dis. Child.* **71**:162-170 (Feb.) 1946.

55. Adams, J. M., and Smith, N.: Clinical Trial of Gamma Globulin in the Prevention of Common Respiratory Diseases, *Proc. Soc. Exper. Biol. & Med.* **63**:446-449 (Nov.) 1946.

revealed evidence of infection by the complement fixation test in 40 per cent of a variety of gulls, terns, pelicans and other shore birds. An ornithosis-like agent was isolated from birds of the willet species.

Vaporized triethylene glycol has a definite but limited value in sterilizing clouds of meningopneumonitis and psittacosis viruses suspended in the air of rooms.⁶⁷ Some of the virus escapes destruction, however, so that the method, while partly effective, is not wholly reliable. For epidemiologic control, it is better to stop the spread of infection by eliminating its source.

In a review⁶⁸ of the merits of various measures to control air-borne infection in general, it is recommended that the use of either ultraviolet rays or triethylene glycol aerosol must be supplemented by measures such as oiling to control dust in order to be effective. In several instances, aerosol treatment failed to reduce the incidence of air-borne infection. The committee does not recommend the general use of these disinfecting devices until further work has been done.

Pneumococcic Pneumonia.—In a series of papers in the September issue of the *American Journal of Hygiene*, Hodges and MacLeod describe epidemic pneumococcic pneumonia over a two and a half year period in a military camp. *Pneumococcus* type II predominated, but types 1, 5, 7, 12 and 14 all showed similar epidemiologic behavior. The person to person spread was greatest in classrooms, and the same incidence of the types of pneumococci was found in carriers as in the dust of rooms. The carrier rates were higher in winter, but in general they showed no close relation to the number of cases of pneumonia except those of types 4 and 12. Vaccination with specific polysaccharides reduced the carrier rate. There was no evidence to favor age, chilling or fatigue as important predisposing factors in causing pneumonia. One case of pneumonia occurred to every ten mild infections of the respiratory tract.

Wood and his associates⁶⁹ present evidence to show that phagocytosis of pneumococci may occur without the agency of a specific antibody or opsonin. Phagocytosis occurs in the pneumonic lung during sulfonamide therapy by direct action of phagocytes on the pneumococci. Direct phagocytosis probably also accounts for the rapid disposal of inhaled pathogenic bacteria. The authors believe, as others do, that

67. Rosebury, T.; Meikeljohn, G.; Kingsland, L. C., and Boldt, M. H.: Disinfection of Clouds of Meningopneumonitis and Psittacosis Viruses with Triethylene Glycol Vapor, *J. Exper. Med.* **85**:65-76 (Jan.) 1947.

68. Recent Studies on Disinfection of Air in Military Establishments, Committee on Sanitary Engineering, National Research Council, *Am. J. Pub. Health* **37**:189-198 (Feb.) 1947.

69. Wood, W. B.; Smith, M. R., and Watson, B.: Studies on the Mechanism of Recovery in Pneumococcal Pneumonia: IV. The Mechanism of Phagocytosis in the Absence of Antibody, *J. Exper. Med.* **84**:387-401 (Oct.) 1946.

Kotin⁶² observed 5 patients with severe viral pneumonia who apparently contracted the disease from a sixth member of the family. No other disease, mild or severe, occurred in equally exposed relatives or in the community at the time. Since all 6 patients were female and genetically related, a hereditary susceptibility to the infection is suggested. A genetic influence on susceptibility to the common cold was mentioned on a previous page.

Holmes reports⁶³ neurologic complications as acute polyneuritis, meningitis and encephalitis in patients with viral pneumonia.

The Pneumonia of Erythema Multiforme Exudativum.—By curious coincidence which occasionally occurs, four groups of observers report studies on pneumonia closely resembling viral pneumonia in cases of erythema multiforme exudativum.⁶⁴ It is characterized by a mononuclear cell exudate and is probably an integral part of the disease, presumably caused by a virus. The disease is a systemic one in which the lungs may be involved and is probably the same as Stevens-Johnson disease.^{64c,d} It has been called dermatostomatitis and mucocutaneous fever, and it may be mistaken for Vincent's disease if fusospirochetal bacteria are present.

Psittacosis and Ornithosis.—Meyer and Eddie⁶⁵ report 2 more cases of psittacosis in which penicillin was therapeutically effective. Large amounts of penicillin, 320,000 units daily, are essential for success. They also report the existence of human carriers. Psittacosis virus was present in the pharyngeal secretions of 1 person for eight years. Contagiousness is apparently of a low order, since no other persons near these carriers contracted the infection.

Because of the presence of ornithosis in several species of birds thus far examined, it was predictable that others would be found. Studies by Pollard,⁶⁶ suggested by the presence of the disease in Fulmar petrels,

62. Kotin, E. H.: Probable Genetic Susceptibility to Viral Pneumonia, *Ann. Int. Med.*, to be published.

63. Holmes, J. M.: Neurological Complications in Atypical Pneumonia, *Brit. M. J.* **1**:218-220 (Feb. 8) 1947.

64. (a) Stanyon, H. H., and Warner, W. P.: Mucosal Respiratory Syndrome, *Canad. M. A. J.* **53**:427-434 (Nov.) 1946. (b) Association of Pneumonia with Erythema Multiforme Exudativum, Commission on Acute Respiratory Disease, *Arch. Int. Med.* **78**:687-710 (Dec.) 1946. (c) Wentz, H. S., and Seiple, H. H.: Stevens-Johnson Syndrome: A Variation of Erythema Multiforme Exudativum (Hebra); Report of Two Cases, *Ann. Int. Med.* **26**:277-282 (Feb.) 1947. (d) Soll, S. N.: Eruptive Fever with Involvement of the Respiratory Tract, Conjunctivitis, Stomatitis and Balanitis, *Arch. Int. Med.* **79**:475-500 (May) 1947.

65. Meyer, K. F., and Eddie, B.: The Knowledge of Human Virus Infections of Animal Origin, *J. A. M. A.* **133**:822-828 (March 22) 1947.

66. Pollard, M.: Ornithosis in Sea-Shore Birds, *Proc. Soc. Exper. Biol. & Med.* **64**:200-202 (Feb.) 1947.

occurred in 4.6 per cent. Dissemination occurred in only 1 per cent of white patients with clinically evident diseases, which amounts to 0.25 per cent for the total number of recognized infections. The incidence of dissemination is over ten times higher in Negroes.

Studies⁷³ in an army camp in the southwestern area of the United States confirm previous observations that dust is the chief mode of conveyance of infection. In such areas, grassing or oiling the surface helps to control the infection. Although the disease is generally believed not to be contagious, experiments show that it is possible to transmit infection from man to animal and from animal to animal by the intra-bronchial inoculation of the spherules.⁷⁴

Pulmonary Calcification from Histoplasmosis.—The frequency of pulmonary calcification, miliary or otherwise, as detected roentgenographically in persons in the central area of the United States in whom the reaction to the tuberculin skin test is negative has often given rise to controversy. Among 64 persons studied⁷⁵ calcification was not noted among any of those who reacted only to tuberculin, but 93 per cent of those with calcified areas showed reaction to histoplasmin alone and in 2 instances to both histoplasmin and tuberculin. The results suggest, as previous studies have, that pulmonary calcification in the central United States is most often caused by the agent of histoplasmosis, assuming that the test is a specific one.

Hemolytic Streptococcic Pharyngitis.—Rantz and his associates⁷⁶ made extensive studies of hemolytic streptococcic sore throat in soldiers, amplifying their previous reports. Streptococci of types 3, 17, 19, 30, 36 and 46 caused most of the attacks, and types 3, 17, 19 and 30 caused more severe disease with cutaneous rash than the others. The disease lasted only four days in 86 per cent of the cases. The severity was not related to the presence or absence of tonsils, to the severity of cervical adenitis or to the amount of exudate, but patients with an exanthem were sick longer. Therapy with sulfadiazine and penicillin, alone and in combination, had but slight effect on shortening the disease or in eradicating hemolytic streptococci from the nose and throat.

73. Smith, C. E.; Beard, R. R.; Rosenberger, H. G., and Whiting, E. G.: Effect of Season and Dust Control on Coccidioidomycosis, *J. A. M. A.* **132**:833-838 (Dec. 7) 1946.

74. Rosenthal, S. R., and Routien, J. B.: The Infectiousness of Coccidioidomycosis, *Science* **104**:479 (Nov. 22) 1946.

75. High, R. H.; Zwerling, H. B., and Furcolow, M. L.: Disseminated Pulmonary Calcification, *Pub. Health Rep.* **62**:20-29 (Jan. 3) 1947. Zwerling, H. B., and Palmer, C. E.: Pulmonary Calcification in Relation to Sensitivity to Histoplasmin, *J. A. M. A.* **134**:691-693 (June 21) 1947.

76. Rantz, L. A.; Spink, W. W., and Boisvert, P. J.: Hemolytic Streptococcic Sore Throat: The Course of the Acute Disease, *Arch. Int. Med.* **79**:272-290 (March) 1947.

the physical changes of the surface of bacteria is probably of great importance in phagocytosis. They imply that their "discovery" of surface phenomena clarifies certain problems in the recovery from infection but fail to mention previous studies of similar import by others. In studies published in 1932,⁷⁰ literature pertaining to the nonspecific relationship of fever and changes in blood protein to phagocytosis and recovery from infection was cited, and experiments were reported which showed that the increase of viscosity of the plasma was an important factor. Furthermore, phagocytosis is not the only important cause of recovery from pneumococcic pneumonia in particular or from infectious disease in general.

Coccidioidomycosis.—Forbus and Bestebreurtje⁷¹ give a comprehensive review of the history of coccidioidomycosis and a discussion of the pathogenesis, clinical features, pathologic anatomy and other details in 95 cases of the severe generalized form as they occurred in the armed forces in the western states from 1941 to 1946. Of the 95 patients studied, 50 died. The disease primarily involves the lungs and in the majority of cases is mild. In a small proportion of patients infection persists and becomes disseminated at any time up to ten years. Of the 6,000 soldiers who were known to have had the disease in endemic areas and perhaps many who had subclinical infections, any are liable to later endogenous dissemination. The generalized form is granulomatous in nature and affects many organs and tissues. In patients who have had erythema nodosum in the early period the generalized form rarely develops. Person to person infection probably does not occur, and it is unlikely that the fungus can live if transplanted to other parts of the country. Contrary to previous views, the occurrence of pulmonary calcification which may be confused with that caused by tuberculosis and histoplasmosis was not observed in Forbus' group, but it may appear in patients who survive long enough. It had previously been reported after coccidioidomycosis by Aronson.

The infection is endemic in the southwestern area of the United States, in South America and in southern Europe. In patients infected in endemic areas the early or later form of disease may develop wherever they may be.

In another study,⁷² 60 per cent of 1,350 persons discovered by the coccidioidin test to be infected were symptomless. Erythema nodosum

70. Reimann, H. A.: The Significance of Fever and Blood Protein Changes in Regard to Defense Against Infection, *Ann. Int. Med.* **6**:362-374 (Sept.) 1932.

71. Forbus, W., and Bestebreurtje, A. M.: *Coccidioidomycosis: A Study of Ninety-Five Cases of the Disseminated Type with Special Reference to the Pathogenesis of the Disease*, *Mil. Surgeon* **99**:653-719 (Nov.) 1946.

72. Smith, C. E.; Beard, R. R.; Whiting, E. G., and Rosenberger, H. C.: Varieties of Coccidioidal Infection in Relation to Epidemiology and Control of Diseases, *Am. J. Pub. Health* **36**:1394-1402 (Dec.) 1946.

without a sulfonamide drug did not prevent these late nonsuppurative complications of unknown nature.

Diphtheria.—According to Anderson⁸⁰ there is no cause for alarm over the suspected appearance of a new highly virulent form of diphtheria bacilli as the cause of the great increase in severe diphtheria in Europe during the war. No new bacilli have been isolated. Diphtheria increased there because of the crowding, hardship, deprivation of food and poor medical care incident to the war. Immunization programs could not be carried out, but there is doubt as to the importance of the preventive role of this procedure, particularly among adults. Fanning, in this respect, reports⁸¹ a severe outbreak of diphtheria in a school in which 94 per cent of the students had been previously immunized and 80 per cent were "Shick negative." The disease, therefore, may occur in a supposedly immunized community and may be severe in previously immunized persons, and the Shick test is not always reliable as an indicator of immunity.

In the United States and Canada diphtheria has increased in incidence since 1944, probably because of the natural epidemic behavior of the disease.

Although penicillin has no effect on the clinical course of diphtheria, it is said to reduce the duration of the convalescence and the carrier rate if given in doses of 120,000 or preferably 240,000 units daily for twelve days.⁸²

Tuberculosis.—Tuberculosis as a cause of death could be eliminated within a generation by using the methods of control now at hand in a well coordinated attack.⁸³ The death rate already has been reduced by four fifths since 1900. Great progress has been made in the early detection of the disease and in the reduction of chances of becoming infected. The greatest problem at present rests in the control of tuberculosis among Negroes.

Similar views are given by Myers,⁸⁴ who outlines a program for control as adopted in Minneapolis. With a fundamental plan of proved effectiveness, the problem of tuberculosis could be solved. Roentgenograms made of each adult's lungs would detect active infections

80. Anderson, G. W.: Foreign and Domestic Trends in Diphtheria, *Am. J. Pub. Health* **37**:1-12 (Jan.) 1947.

81. Fanning, J.: Outbreak of Diphtheria in a Highly Immunized Community, *Brit. M. J.* **1**:371-372 (March 22) 1947.

82. Wienstein, L.: The Treatment of Acute Diphtheria and the Chronic Carrier State with Penicillin, *Am. J. M. Sc.* **213**:308-314 (March) 1947.

83. Wiping Out Tuberculosis in Our Time, *Statist. Bull. Metrop. Life Insur. Co.* **27**:1-3 (Nov.) 1946.

84. Myers, J. A.: The Establishment and Use of Fundamental Procedures in Tuberculosis Control, *Pub. Health Rep.* **61**:1563-1583 (Nov. 1) 1946.

Persons who have mild or subclinical infections of the upper respiratory tract or those who have had "missed cases" caused by group A hemolytic streptococci may serve as carriers and disseminators of this germ, according to Lemon and Hamburger.⁷⁷ In an epidemiologic study in one season, "missed cases" probably comprised from 67 to 94 per cent of carriers. Mere "contact" carriers or those with no serologic evidence of infections were uncommon. Nasal carriers are more apt to transmit infection than those in whom the cocci are present only in the throat.

The reaction to the Dick test was positive in 28 per cent of soldiers who had acute infection of the respiratory tract.⁷⁸ The reaction was positive in both the viral type of disease and in that caused by hemolytic streptococci, which fact, the authors believe, indicates a lack of relationship between the reaction and specific immunity to infection with streptococci. The reaction to the Dick test is believed to become positive as a result of exposure to the bacteria and the development of acquired hypersensitivity to its products, but such a reaction does not necessarily indicate a natural susceptibility to the toxin.

In a study of the "poststreptococcic state",⁷⁹ certain patients who had recovered from an infection caused by hemolytic streptococci remained febrile for some time after; in others fever, arthritis, carditis, pneumonia, or lymphadenitis developed in early convalescence. Glomerulonephritis was not encountered. These apparent sequels were noted in 20 per cent of all cases of hemolytic streptococcic infection and could not be demonstrated to be the result of local extension of the initial process in the throat or the invasion of remote areas by the bacteria. In patients with arthritis and carditis the condition was indistinguishable from that of classic rheumatic fever. The pneumonia which was observed resembled viral pneumonia but for the presence of leukocytosis and a rapid sedimentation rate. The pneumonia presumably is akin to that which may accompany rheumatic fever but is milder. It is not caused primarily by the hemolytic streptococcus as a true streptococcic pneumonia.

The studies emphasize the seriousness of hemolytic streptococcic infections of the respiratory tract, especially since therapy with large amounts of sodium salicylate and a short course of penicillin with or

77. Lemon, H. M., and Hamburger, M.: Missed Cases and Contact Carriers Among Nasal Carriers of Beta Hemolytic Streptococci, *J. Immunol.* **54**:189-196 (Oct.) 1946.

78. Rantz, L. A.; Boisvert, P. J., and Spink, W. W.: Dick Test in Military Personnel with Special Reference to Pathogenesis of Skin Reaction, *New England J. Med.* **235**:39-42 (July 11) 1946.

79. Rantz, L. A.; Boisvert, P. J., and Spink, W. W.: Hemolytic Streptococcic Sore Throat: The Poststreptococcic State, *Arch. Int. Med.* **79**:401-435 (April) 1947.

patients described died, a fact which indicates the serious import of rheumatic pneumonia. The condition occurs far oftener in rheumatic fever than other forms of pneumonia and can be recognized relatively easily. Both Seldin⁸⁹ and Mossberger,⁹⁰ like Rantz, point out certain resemblances to viral pneumonia, but rheumatic pneumonia almost certainly consists of the specific reaction of the lung during rheumatic fever.

According to Bruetsch⁹¹ the brain may be involved in the rheumatic state. He reports rheumatic vascular obliterations in the smaller meningeal and cortical branches of the cerebral vessels which can be found only by making serial sections. While there is little doubt that the cerebral vessels may be involved as well as other vessels in the body, one may question the author's view, as skeptical discussers of his paper have, incriminating rheumatic disease as an important cause of mental disease. Breutsch reports histologic evidence of rheumatic brain disease in 9 per cent of patients with schizophrenia. According to some of the discussers the lesions are nonspecific and are found in other conditions as well.

In testing Guerra's theory that the symptoms of rheumatic fever are influenced favorably after the inhibition of hyaluronidase by sodium salicylate, Pike⁹² was unable to show that the drug had any inhibiting effects on streptococcic hyaluronidase in vitro. Others,⁹³ however, show that sodium salicylate does inhibit the spreading effect of hyaluronidase in the animal body. Greater amounts of salicylate are needed to accomplish the effect in the test tube. An inhibiting substance able to neutralize an enzyme (hyaluronidase) made by hemolytic streptococci was demonstrated in the blood of many persons but particularly in those with rheumatic fever.⁹⁴ The matter obviously needs further study.

Other studies^{94a} which deal with the pathogenesis of rheumatic fever involve hyaluronic acid in so-called albumin-bacterioplasm con-

89. Seldin, D. W.; Kaplan, H. S., and Bunting, H.: Rheumatic Pneumonia, *Ann. Int. Med.* **26**:496-520 (April) 1947.

90. Mossberger, J. I.: Rheumatic Pneumonia: Report of Two Cases, *J. Pediat.* **30**:113-122 (Feb.) 1947.

91. Bruetsch, W. L.: Rheumatic Brain Disease, *J. A. M. A.* **134**:450-453 (May 31) 1947.

92. Pike, R. M.: Failure of Sodium Salicylate to Inhibit Hyaluronidase in Vitro, *Science* **105**:391 (April 11) 1947.

93. Dorfman, A.; Reimers, E. J., and Ott, M. L.: Action of Sodium Salicylate on Hyaluronidase, *Proc. Soc. Exper. Biol. & Med.* **64**:357-360 (March) 1947.

94. Friere, G. J., and Wenner, H. A.: On the Occurrence in Human Serum of an Inhibitory Substance to Hyaluronidase Produced by a Strain of Hemolytic Streptococcus, *J. Infect. Dis.* **80**:185-193 (March-April) 1947.

94a. Schultz, M. P., and Rose, E. J.: Albumin-Bacterioplasm Conjugates with Special Reference to the Etiology of Rheumatic Fever, *Pub. Health Rep.* **62**:1009-1022 (July 11) 1947.

responsible for the spread of the disease. Patients with such infections would be isolated and treated. The tuberculin test would serve to discover the remainder of persons with primary tuberculosis. In a decade after the use of this plan, the author predicts, the number of beds needed for tuberculous patients would be far less, and in another decade the disease could be suppressed to an irreducible minimum. The responsibility for these procedures lies with public health officials.

Hilleboe⁸⁵ calls attention to the controversial issues in the control of tuberculosis, as the diagnostic value of the tuberculin test, the accuracy of roentgenologic interpretation and the value of vaccination with BCG.

At a recent conference⁸⁶ the use of BCG vaccine was discussed. Vaccination, all agree, is harmless; it confers increased resistance to tuberculosis and converts a large percentage of nonreactors to tuberculin into reactors. But since information about the degree and duration of the immunity given by the vaccine is incomplete, BCG should not be made available commercially at present. According to a report from Norway,⁸⁷ BCG vaccine gives protection against tuberculosis in 75 to 95 per cent of subjects. According to Birkhaug,^{87a} Scandinavian physicians regard BCG vaccine as the best measure of controlling tuberculosis in young adults.

The use of streptomycin for tuberculosis has been discussed.

RHEUMATIC FEVER

Rheumatic fever often manifests itself in deceptive forms.⁸⁸ It may be encountered with no articular symptoms, as a monarticular involvement or as arthritis of the hands or feet, with prodromal aching for days to weeks before the typical symptoms appear; there may be no fever during the acute stage, and it may begin with pericarditis or pneumonia.

Two other groups of observers like Rantz, as discussed in a preceding section, comment on our inadequate knowledge of "rheumatic pneumonia." One group⁸⁹ did not encounter mild, fleeting pulmonary lesions as described by Rantz⁷⁹ in the poststreptococcic state. Instead, all 6

85. Hilleboe, H. E.: Controversial Issues in Tuberculosis Control, *Pub. Health Rep.* **61**:1561-1563 (Nov. 1) 1946.

86. Report of a Conference on BCG Vaccination, *Pub. Health Rep.* **62**:346-350 (March 7) 1947.

87. Hertzberg, G.: Recent Experience with BCG Vaccination in Norway, *Tubercle* **28**:1-10 (Jan.) 1947.

87a. Birkhaug, K.: BCG Vaccination in Scandinavia: Twenty Years of Uninterrupted Vaccination Against Tuberculosis, *Am. Rev. Tuberc.* **55**:234-249 (March) 1947.

88. Sokolow, M., and Snell, A. M.: Atypical Features of Rheumatic Fever in Young Adults, *J. A. M. A.* **133**:981-989 (April 5) 1947.

Rheumatoid Arthritis.—In a series of papers, Wallis⁹⁸ concludes that rheumatoid arthritis is not proved to be of bacterial origin, especially as regards hemolytic streptococci. The serologic reactions which have thus far been studied and thought to be of aid in signifying certain causative agents are of doubtful value and probably represent the non-specific enhancement of normally present antibodies. By electromyographic studies,^{98a} further evidence accrues of an involvement of the neuromuscular system to account for certain neurologic symptoms and signs characteristic of rheumatoid arthritis and probably partly explains its pathogenesis. There may also be lesions of the lower motor neurons, as in certain other diseases. Histologic changes were found in the lateral projections of the anterior horns of the cord.

ENTERIC DISEASES

Shigellosis, or Bacillary Dysentery.—Attempts were made to infect volunteers with dysentery bacilli.⁹⁹ There was no constant relation between invasiveness of the bacteria in experimental animals and that in man. Strains virulent for animals were not always infective in man, and the opposite was noted. Relatively large doses of ten billion bacilli of the Flexner W strain caused only slight cramps in 1 volunteer and in 3 others caused nausea, headache, chills and diarrhea. None had fever, and in 1 symptoms lasted ten days. In one experiment a dose of fifty billion bacilli caused only mild headache, anorexia and slight cramps. Other strains of the Flexner type of bacilli caused symptoms typical of dysentery twelve hours after ingestion in about half of the subjects, and in many no symptoms at all developed. Obviously, other factors besides the presence of bacilli alone are needed before disease occurs. In most successful infections the "incubation" period was less than twenty-four hours, diarrhea appearing eighteen to twenty-four hours after ingestion of the inoculum. Nausea and vomiting, the chief early symptoms in the volunteers, when encountered in naturally infected persons would hardly lead to a suspicion or a diagnosis of shigellosis and certainly not of "dysentery."

98. Wallis, A. D.: Rheumatoid Arthritis: I. Introduction to a Study of Its Pathogenesis, *Am. J. M. Sc.* **212**:713-715 (Dec.) 1946; II. Non-Specific Serologic Reactions, *ibid.* **212**:716-717 (Dec.) 1946; III. The Pneumococcus Antibodies, *ibid.* **212**:718-722 (Dec.) 1946; IV. Hemolytic Streptococcus Precipitin Reactions, *ibid.* **213**:87-93 (Jan.) 1947; V. The Agglutination of Hemolytic Streptococci, *ibid.* **213**:94-96 (Jan.) 1947.

98a. Morrison, L. R., and others: The Neuromuscular System in Rheumatoid Arthritis: Electromyographic and Histologic Observations, *Am. J. M. Sc.* **214**:33-49 (July) 1947.

99. Shaughnessy, H. J.; Olsson, R. C.; Bass, K.; Friewer, F., and Levinson, S. O.: Experimental Human Dysentery: Polyvalent Dysentery Vaccine in Its Prevention, *J. A. M. A.* **132**:362-368 (Oct. 19) 1946.

jugates. Apparently, extracts of embryonal connective tissue and human serum combine in some way with the products of hemolytic streptococci to form toxic substances. These substances cause cardiac lesions akin to those of rheumatic fever when injected into animals. They cause pain at the site of injection, systemic disturbance suggestive of extensive injury to tissue and occasionally the major manifestation of the disease in patients convalescent from rheumatic fever and systemic reactions of fever and increased number of leukocytes in nonrheumatic control persons. What seems to be of especial significance is that after gradually increasing doses the development of tolerance or of increased resistance was noted both in rheumatic and in control persons.

According to Harris' observations,⁹⁵ massive doses of salicylates, once recommended for the treatment of acute rheumatic fever, do not suppress the inflammatory process.

Dry, Butt and Scheifley⁹⁶ comment on the influence of paraaminobenzoic acid on diverse biologic activities, including its antisulfonamide action, its inhibiting effect on growth of rickettsia and its growth-promoting effects. In their experiments paraaminobenzoic acid when given with sodium salicylate during the course of therapy of rheumatic fever greatly raised the level of salicylate in the blood. Paraaminobenzoic acid apparently was therapeutically effective in lowering the fever and lessening the arthralgia in a few cases of rheumatic fever.^{96a}

Burke⁹⁷ gave three pastilles of 500 units of penicillin daily for a year to 10 rheumatic patients and compared their course with that of 10 untreated patients. Rheumatic manifestations during this period were six times more frequent in the control group, suggesting the value of penicillin as a prophylactic agent. It may be recalled that similar reports were published several years ago about prophylaxis with sulfonamide compounds.

95. Harris, T. N.: The Failure of Massive Salicylate Therapy to Suppress the Inflammatory Reaction in Rheumatic Fever, *Am. J. M. Sc.* **213**:428-487 (April) 1947.

96. Dry, T. J.; Butt, H. R., and Scheifley, C. H.: The Effect of Oral Administration of Para-Aminobenzoic Acid on the Concentration of Salicylates in the Blood: Preliminary Report, *Proc. Staff Meet., Mayo Clin.* **21**:497-504 (Dec. 24) 1946.

96a. Rosenblum, H., and Fraser, L. E.: Effect of Para-Aminobenzoic Acid on Fever and Joint Pains of Acute Rheumatic Fever, *Proc. Soc. Exper. Biol. & Med.* **65**:178-180 (June) 1947.

97. Burke, P. J.: Penicillin Prophylaxis in Acute Rheumatism, *Lancet* **1**:255-256 (Feb. 15) 1947.

Shigella flexneri III was the commonest type. The chief sources of infection were food handled by carriers on board ship, contaminated food eaten ashore, convalescent carriers on board and the domestic use of contaminated sea water. Salmonella infections were usually milder than shigellosis and came from the meat of turkeys, chickens and salmon. Measures for the prevention and management of outbreaks on shipboard are outlined.

A progress report of advances in knowledge of dysentery and its causative bacilli gained between 1942 and 1946 was published.¹⁰² Particular attention is given to the confused problem of classification. Dysentery and diarrhea exceeded malaria as the most common "tropical" disease in our armed forces between 1942 and 1945.¹⁰³

Viral Dysentery.—English physicians describe¹⁰⁴ coincident epidemics of Sonne bacillary dysentery and nonspecific gastroenteritis among nurses. The former was explosive in nature, and in the latter the cases were distributed over several months as previously described in other epidemics of "viral dysentery." Clinically the two diseases were indistinguishable. Bacillary dysentery was controlled with sulfaguanidine; viral dysentery was not. The authors agree that a virus is the most probable cause of the nonspecific gastroenteritis. One may object to the suffix "itis" implying inflammation, since fever is often absent, the stools do not contain blood or pus and the leukocyte count is normal.

Other British physicians^{104a} describe an outbreak in which both infants and adults were sick.

Typhoid.—In Stuart and Pullen's analysis¹⁰⁵ of 360 cases of typhoid, in only 40 per cent had the disease been correctly diagnosed when the patients entered the hospital. Symptoms referable to the respiratory tract most often were confusing since 87 per cent of patients had coryza, 86 per cent coughed, 84 per cent had sore throat, rales were heard in 64 per cent and 12 per cent had pneumonia. The mortality rate was 13 per cent. Sulfonamide therapy was of no value.

102. Weil, A. J.: Dysentery: A Progress Report for the Years 1942 to 1946, *J. Immunol.* **55**:363-405 (April) 1947.

103. Saper, J. J.: Tropical Diseases in Veterans of World War II, *New England J. Med.* **235**:843-836 (Dec. 12) 1946.

104. Martin, L., and Wilson, M. M.: Sonne Dysentery and Non-Specific Gastro-Enteritis in a Hospital, *Lancet* **1**:553-555 (April 26) 1947.

104a. Cook, G. T., and Marmion, B. P.: Gastroenteritis of Unknown Etiology: An Outbreak in a Maternity Unit, *Brit. M. J.* **2**:446-450 (Sept. 20) 1947.

105. Stuart, B. M., and Pullen, R. L.: Typhoid: Clinical Analysis of Three Hundred and Sixty Cases, *Arch. Int. Med* **78**:629-661 (Dec) 1946.

There was no evidence of the value of vaccine prepared with either heat-killed or irradiated bacilli in the prevention of experimentally induced shigellosis. Attacks of dysentery and the carrier state were easily controlled with sulfadiazine. Interest in the presence of antibody against dysentery bacilli in the stools of patients with dysentery, begun in 1922, was revived by the studies of Burrows, as yet unpublished, and by those of Harrison and Banvard.^{99a} The coproantibody, as it is called, was found to be present as early as the third day of disease, to increase in titer up to about the ninth day and then to disappear rapidly. The development of agglutinin within three days is remarkably soon for any disease. This is in contrast with antibody in the blood, which does not appear as a rule before recovery is established and which persists for many weeks. The presence of specific antidysentery bacillus fecal agglutinin in 97 per cent of patients suggests that their demonstration is a valuable diagnostic aid. The existence of coproantibody may also explain certain puzzling phases of immunity against cholera, bacillary dysentery and salmonella enteritis and may serve as a mechanism which aids in recovery from enteric infections.

The old controversy about the relationship of bacillary dysentery to chronic ulcerative colitis again arises. In Felsen and Wolarsky's follow-up study¹⁰⁰ of an epidemic of bacillary dysentery in 1934, 10.7 per cent of victims were found to have had ulcerative colitis or ileitis nine to twelve months later. A new study was prompted by the great number of attacks of dysentery in military personnel during the war. In one group of 61 patients with ulcerative colitis studied five to thirty-one months after an acute attack of dysentery, most of them showed inflammation of the bowel wall, and dysentery bacilli were recovered from 10 per cent. The authors believe that chronic ulcerative colitis and ileitis are the result of acute bacillary dysentery. While no one doubts that shigellosis may lead to chronic colitis in a small percentage of patients, one can hardly agree that bacillary dysentery is the cause of most cases of nonspecific ulcerative colitis.

Study was made of several epidemics of gastroenteritis on ships during the war.¹⁰¹ They were caused in about equal numbers by *Shigella*, *Salmonella* and unknown agents, probably viruses (viral dysentery). *Staphylococci* may have been operative in some of the milder outbreaks but were not established as a cause. Of the *Shigella* group,

99a. Harrison, P. E., and Banvard, J.: Coproantibody Excretion During Enteric Infections, *Science* **106**:189 (Aug. 29) 1947.

100. Felsen, J., and Wolarsky, W.: Bacillary Dysentery and Chronic Ulcerative Colitis in World War II, *Science* **105**:213 (Feb. 21) 1947.

101. Meyers, W. A.: Gastroenteritis Aboard Ship: Common Types Encountered and the Prevention and Control of Outbreaks, *Pub. Health Rep.* **61**:1853-1858 (Dec. 20) 1946.

disease. It was suggested elsewhere that perhaps vibrios exist in carriers in an unrecognizable variant form. They propose a new classification for *Vibrios comma*, as follows: type A, AB, AC and ABC, dependent on a combination of type-specific antigens, the letters to replace the Japanese eponyms in current use. Type A is a newly recognized specific form. By using this method of classification, Burrows identified nine strains of *V. comma* obtained by Reimann¹¹⁰ from cholera patients, as follows: three were of type AB (Ogawa type), two were type AC (Inaba), two were type ABC (Hikojima) and two contained antigen B but lacked antigen A. The last two, according to Burrows, are not true cholera vibrios. It was somewhat surprising to find so many varieties of *V. comma* in patients in a local community. The question arises of whether one variety initiates an outbreak and other types arise later by type transformation or as variant forms or whether various types are always present and cause simultaneous infections in an epidemic.

Thousands of cases of cholera were reported from Korea, China and India in 1946.¹¹¹ An epidemic occurred in Egypt in the autumn of 1947.

OTHER BACILLARY DISEASES

Chronic Brucellosis.—Evans reviews¹¹² the history of the development of knowledge of brucellosis in this country beginning with Craig's recognition of the first case in 1906. She estimates the existence at present of 40,000 cases of acute or chronic brucellosis in the United States. Perhaps 4,000,000 persons are infected annually, but only a small percentage become sick enough to seek medical aid.

According to Darley and Gordon,¹¹³ the intradermal test is the reaction most consistently positive in chronic brucellosis, but it does not distinguish past from existing infection. In applying the test to a large number of patients with obscure conditions, they were unable to find brucellosis as an important cause of allergic disturbances, chronic arthritis or psychoneurosis. The most frequent symptoms in 74 patients with chronic brucellosis were fatigue, generalized aches and pains, headache, digestive disturbance and low grade fever. Positive agglutination reaction occurred in many of these patients. One can hardly agree with

110. Reimann, H. A.: Further Note on the Classification of *Vibrios* from the 1945 Cholera Epidemic in Chungking, *Am. J. Trop. Med.* **27**:503 (July) 1947.

111. Foreign Reports, *Pub. Health Rep.* **62**:622 (April 25) 1947.

112. Evans, A. C.: Brucellosis in the United States, *Pub. Health Rep.* **37**:139-151 (Feb) 1947.

113. Darley, W., and Gordon, R. W.: *Brucella Sensitization: A Clinical Evaluation*, *Ann. Int. Med.* **26**:528-541 (April) 1947.

Perforation of the ileum in typhoid was given special study by Dunkerly.¹⁰⁶ The incident occurred in 1 per cent of 1,077 patients, some of them ambulatory. The mortality rate was 55 per cent in patients operated on. He recommends a full diet to prevent the accident.

A case of typhoid osteomyelitis of the skull which developed twenty-five years after an attack of typhoid is reported.^{106a} A pure culture of nonviable forms was derived from the lesion, but no typhoid bacilli were present in the bile or the stools, and the reaction to the Widal test was negative. Streptomycin, tyrocidin, gramicidin and acriflavine applied locally and penicillin with a sulfonamide drug and antityphoid vaccination had no influence on the infection.

The residual fraction or supposed impurities of streptomycin were found to be two to five times more effective against *Eberthella typhosa* than purified streptomycin.^{106b}

Cholera.—Although Reimann and his associates¹⁰⁷ were not impressed by the effects of sulfadiazine on cholera, Chu and others,¹⁰⁸ observing the same group of patients in Chungking, felt that the disease was shortened significantly by chemotherapy, as did Chu and Huang concerning other patients in Foochow.

In extensive studies on the bacteriology of cholera Burrows and his associates¹⁰⁹ point out how uncertain is the value of specific vaccination and conclude that previous experience indicates the development of only a low grade of immunity after vaccination. They discuss the difficulties of classifying vibrios, the uncertainty in differentiation on the basis of their chemical constituents and the report that no instance of a chronic carrier of the classic cholera vibrio has been discovered. El Tor vibrios, however, are found in carriers and do cause cholera-like

106. Dunkerly, G. E.: Perforation of the Ileum in Enteric Fever, *Brit. M. J.* **2**:454-457 (Sept. 28) 1946.

106a. Haven, H.: Typhoid Osteomyelitis of the Skull, *Bull. Mason Clin.* **1**: 55-59 (June) 1947.

106b. Hobby, G. L., and Lenert, T. F.: Biological Activity of a Residual Form of Streptomycin Against *Eberthella Typhosa*, *Proc. Soc. Exper. Biol. & Med.* **65**:249-254 (June) 1947.

107. Reimann, H. A., and others: Asiatic Cholera: Clinical Study and Experimental Therapy with Streptomycin, *Am. J. Trop. Med.* **26**:631-647 (Sept.) 1946.

108. Chu, L. W., and Huang, C. H.: Effect of Sulfadiazine on Cholera, *Am. J. Trop. Med.* **26**:821-823 (Nov.) 1946. Chu, L. W.; Huang, C. H.; Chang, C. T., and Kao, H. C.: Sulfonamide Drugs in the Treatment of Cholera, *ibid.* **26**:825-830 (Nov.) 1946.

109. Burrows, W.; Mather, A. N.; Elliott, M. E., and Wagner, S. M.: Studies on the Immunity to Asiatic Cholera: I. Introduction, *J. Infect. Dis.* **79**:159-167 (Sept.-Oct.) 1946. Burrows, W.; Mather, A. M.; McGann, V. G., and Wagner, S. M.: Studies on the Immunity to Asiatic Cholera: II. The O and H Antigenic Structure of the Cholera and Related Vibrios, *ibid.* **79**:168-197 (Sept.-Oct.) 1946.

work needs confirmation or rejection. Tularemia was observed in Austria and in France.^{117a}

Plague.—The mortality rate of plague during an epidemic in Foo-chow was 51 per cent up to July 18, 1944.¹¹⁸ Among 25 patients admitted after July 18 who were treated with sulfadiazine the rate was 20 per cent. Sulfadiazine is said to be the drug of choice.

In a personal communication one of the authors, Dr. L. W. Chu, reports the successful treatment of a patient with pneumonic plague with streptomycin. The infection was contracted in a laboratory. The same author, with Huang, reports excellent effects in the treatment of bubonic plague with sulfadiazine. Bacilli, however, often survive in the bubos. Plague was successfully treated with streptomycin in Argentina.^{118a}

In Africa treatment with sulfathiazole given intramuscularly and sulfadiazine given intravenously gave a mortality rate of only 6.6 per cent in patients treated early.¹¹⁹ In patients treated twenty-four hours or more after the onset of illness the rate was 19.7 per cent. No control patients were used for comparison. All 19 patients with nonbubonic plague died. Grasset reports¹²⁰ success in immunization against plague with living avirulent plague bacilli. No ill effects are recorded.

Eight cases of plague with meningitis were studied¹²¹ among 203 cases of plague in China in 1943 to 1945. One patient had the rare form of primary plague meningitis.

An epidemic of plague occurred in Africa in 1944-1945.¹²² Thousands of cases of plague were reported from Southeast Asia in 1946 and several hundred from South America.¹¹¹ Outbreaks occurred in Turkey and in Palestine in the spring and summer of 1947.^{122a}

117a. Puntigam, F.: Epidemiology of Tularemia in Lower Austria, *Wien. klin. Wchnschr.* **59**:103-105 (Feb. 21) 1947. First Cases of Tularemia in France, *Foreign Letters, J. A. M. A.* **135**:176 (Sept. 20) 1947.

118. Huang, C. H., and Chu, L. W.: Treatment of Bubonic Plague with Sulfadiazine, *Am. J. Trop. Med.* **26**:831-839 (Nov.) 1946.

118a. Videla, C. A.: Clinical Course and Treatment of Bubonic Plague, *Rev. Assoc. Med. argent.* **61**:15-20 (Jan.-Feb.) 1947.

119. Simeons, A. T. W., and Chhatre, K. D.: One Thousand Cases of Bubonic Plague Treated in an Emergency Plague Hospital, *Indian M. Gaz.* **81**:235-246 (June-July) 1946.

120. Grasset, E.: Control of Plague by Means of Live Avirulent Plague Vaccine in Southern Africa (1941-1944), *Tr. Roy. Soc. Trop. Med. & Hyg.* **40**:275-294 (Dec.) 1946.

121. Landsborough, D., and Tunnell, N.: Observations on Plague Meningitis, *Brit. M. J.* **1**:4-7 (Jan. 4) 1947.

122. Davis, D. H. S.: Plague Survey of Ngamiland, Bechuanaland Protectorate During Epidemic of 1944-1945, *South African M. J.* **20**:462-466 (Aug. 24) 1946.

122a. Outbreak of Bubonic Plague, *Foreign Letters, J. A. M. A.* **134**:1040 (July 19) 1947. Bubonic Plague in Haifa, *Medical News, ibid.* **134**:1035 (July 19) 1947.

the authors, however, that chronic brucellosis is a separate clinical entity. It is the chronic form of brucellosis.

Sulfadiazine, penicillin and streptomycin were ineffective in the treatment of patients who acquired brucellosis as accidental laboratory infections.⁵

Glanders.—Six cases of glanders contracted as laboratory infections are reported,¹¹⁴ but the clinical descriptions of them are so different from that of glanders in medical textbooks that several questions arise. No discussion or explanation of this divergence is given, nor was the discrepancy noted editorially.¹¹⁵ Either the books are wrong or they fail to describe the mildest forms, which may be contracted by inhalation of floating bacilli instead of by natural contact infection, or the cases reported were not of glanders. Six persons working with cultures of *Malleomyces mallei* became sick with evidence of pulmonary involvement. The authors report striking persistent leukopenia and relative lymphocytosis as a characteristic feature, yet the lowest count mentioned was 5,000 and the highest lymphocyte percentage 45. In almost all cases the normal count was undisturbed; one count was 10,000 and one 18,000. Diagnosis was based on the known exposure to infection, on the reaction to the skin test and on the agglutinin titer and the fixation of the complement. In no case were glanders bacilli recovered. The question may be raised of whether exposure alone to the bacilli may have caused some of these reactions to become positive. The condition may have been confused with viral pneumonia or malaria or, in 1 case, with brucellosis which had occurred previously. Curiously, sulfonamide therapy was begun in most cases after recovery seemed to be established.

Melioidosis.—The first indigenous case of melioidosis in the United States was discovered in St. Louis.¹¹⁶ The patient had the chronic form, with ulcers and sinuses on the thigh for eight years, during which time nearly eighty operations had been performed for drainage. Various sulfonamide compounds, penicillin and streptomycin were ineffective in therapy. Widespread cautery excision and skin grafting have given the best result to date.

Tularemia.—Jackson¹¹⁷ advocates the treatment of tularemia with bismuth sodium tartrate as preferable to streptomycin. It is cheaper, easier to give and according to his results is more efficient in rapid cure than streptomycin. No details are given in the paper, and the

114. Howe, C., and Miller, W. R.: Human Glanders: Report of Six Cases, *Ann. Int. Med.* **26**:93-115 (Jan.) 1947.

115. Human Glanders, editorial, *J. A. M. A.* **133**:622 (March 1) 1947.

116. McDowell, F., and Varney, P. L.: Melioidosis: Report of First Case from the Western Hemisphere, *J. A. M. A.* **134**:361-362 (May 24) 1947.

117. Jackson, W. W.: Further Report on the Use of Bismuth Sodium Tartrate Intravenously in the Treatment of Two Hundred and Three Additional Patients with Tularemia, *Am. J. M. Sc.* **213**:358-361 (March) 1947.

Smallpox virus survived for thirty-five days when exposed to daylight and for eighty-four days when kept in the dark.¹³⁸ The virus remained viable for a year in crusts of skin kept in the dark at room temperature. These observations show that smallpox may be contracted from sources remote from patients for long periods.

Mumps.—With rare exception, persons whose blood contains complement-fixing antibodies for mumps virus are resistant to infection by natural exposure.¹³⁹ Inapparent infections with mumps are undoubtedly common and probably represent about one third of all cases, since about two thirds of tested persons in large groups have antibody in their blood. The skin test in adults gives an even more sensitive indication of past infection. Persons who exhibit an erythematous dermal reaction to inactivated mumps virus may be regarded as resistant to mumps within an error of 2 to 10 per cent depending on the intensity of the reaction. The skin test itself may evoke a degree of resistance to mumps.

Formalized virus vaccine increased resistance to mumps in about half of a group of vaccinated persons.¹⁴⁰ An improved vaccine against mumps prepared by attenuation during prolonged serial cultivation in embryonated eggs gives promise of greater practical value.¹⁴¹ Vaccine has been prepared from egg cultures which induces specific immunity in monkeys.¹⁴² Swelling of the parotid gland in inoculated monkeys which were vaccinated was less as compared with that in control animals. An unusual case of primary viral mastitis from mumps was reported.¹⁴³

138. Downie, A. W., and Dumbell, K. R.: Survival of Variola Virus in Dried Exudate and Crusts from Smallpox Patients, *Lancet* **1**:550-553 (April 26) 1947.

139. Maris, E. P.; Enders, J. F.; Stokes, J., Jr., and Kane, L. W.: Immunity in Mumps: Correlation of Presence of Complement-Fixing Antibody and Resistance to Mumps in Human Beings, *J. Exper. Med.* **84**:323-339 (Oct.) 1946. Enders, J. F.; Kane, L. W.; Maris, E. P., and Stokes, J., Jr.: Immunity in Mumps: Correlation of Presence of Dermal Hypersensitivity and Resistance to Mumps, *ibid.* **84**:341-364 (Oct.) 1946.

140. Stokes, J., Jr.; Enders, J. F.; Maris, E. P., and Kane, L. W.: Immunity in Mumps: VI. Experiments on the Vaccination of Human Beings with Formalized Mumps Virus, *J. Exper. Med.* **84**:407-428 (Nov.) 1946.

141. Enders, J. F., and others: Alteration of Virulence with Retention of Antigenicity of Mump Virus After Passage in the Embryonated Egg, *J. Immunol.* **54**:283-291 (Nov.) 1946.

142. Habel, K.: Preparation of Mump Vaccines and Immunization of Monkeys Against Experimental Mumps Infection, *Pub. Health Rep.* **61**:1655-1664 (Nov. 15) 1946.

143. Lee, C. M.: Primary Virus Mastitis from Mumps, *Virginia M. Monthly* **73**:327-328 (July) 1946.

Wayson¹²³ resurrects the controversy as to whether (a) plague among the rodents of this country is "spreading" eastward or whether (b) investigations to detect plague are spreading eastward. On the first assumption, plague has "spread" to South America since it was recently discovered in ground squirrels of Peru,¹²⁴ but, in keeping with the second assumption, investigators discovered sylvatic plague there, just as it was discovered when sought in the United States and in Africa. It is likely that plague was always present wherever certain rodents are found and is not necessarily spreading. It has not been reported east of Minnesota or Kansas,^{124a} where there are no colonizing squirrels and prairie dogs which are reservoirs of infection.

According to Wayson plague is perpetuated from year to year in infected fleas which survive the winter. He found no evidence that rodent carriers of infection are factors in enzootic plague, although both hibernating and nonhibernating animals occasionally are found to be infected.

Leprosy.—Faget¹²⁵ points out that leprosy is being introduced constantly into the western states by oriental and Mexican immigrants but that a few indigenous cases occur. The most active focus is found in the Gulf Coast States. It is communicable in Texas, where most of 226 patients from that state were infected. Leprosy was brought to Florida before 1776 by African slaves.

Leprosy is of greatest menace to members of a household containing a patient. Patients prefer the euphemism "Hansen's disease" to the term leprosy. "Promin" (sodium p,p'-diaminodiphenylsulfone-n,n'-dextrose sulfonate) is replacing chaulmoogra oil in therapy.

Scleroma and Rhinoscleroma.—There is doubt as to whether the bacterium *Klebsiella rhinoscleromatis*, which resembles Friedländer bacilli, is the cause of this disease. In new studies¹²⁶ it was again isolated from 6 patients who were genetically related members of a family, and the complement fixation test suggested its etiologic relation.¹²⁷ It is uncertain if scleroma is a hereditary condition causing lesions inhabited by the bacillus in question as a saprophyte or if, as in leprosy, members

123. Wayson, N. E.: Plague: Field Studies in Western United States During Ten Years (1936-1945), Pub. Health Rep. **62**:780-791 (May 30) 1947.

124. Macchiavello, A.: Sylvatic Plague Found in Peru, Medical News, J. A. M. A. **133**:957 (March 29) 1947.

124a. Plague Infection Reported in the United States in 1946, Pub. Health Rep. **62**:1336 (Sept. 12) 1947.

125. Faget, G. H.: The Story of the National Leprosarium, Pub. Health Rep. **61**:1871-1983 (Dec. 27) 1946.

126. Levine, M. G.; Hoyt, R. E., and Paterson, J. E.: Scleroma: An Etiological Study, J. Clin. Investigation **26**:281-286 (March) 1947.

127. Levine, M. G., and Hoyt, R. E.: Scleroma: Complement Fixation Test, Proc. Soc. Exper. Biol. & Med. **65**:70-72 (May) 1947.

believed to be kept active from year to year in monkeys who have the jungle type of yellow fever and is probably transmitted by *Aedes africanus* or *Aedes simpsoni*. The latter may transmit the disease to man, from whom the virus is acquired and spread to others by *A. aegypti*.

Pretibial Fever, or Fort Bragg Fever.—In 1942 Daniels and Grennan reported a benign infectious disease among soldiers in North Carolina. It was believed to be a hitherto undescribed disease, but dengue or some other known infection was suspected by certain critics. Similar outbreaks occurred in 1943 and 1944. The term pretibial fever was facetiously translated as meaning "hot shins," and this is inaccurate since the eruption also occurs on the arms and elsewhere. Now Tatlock¹⁴⁹ brings forth evidence of a "new" virus as the cause. The agent was recovered from the blood of patients and established in laboratory animals and embryonated eggs. The virus when inoculated into volunteers induced a clinical response typical of the naturally acquired disease.

DISEASES OF PRESUMED VIRAL ORIGIN

Viral Hepatitis.—Alsted¹⁵⁰ describes a form of malignant hepatitis in Denmark, particularly in women over 45 years of age. The mortality rate was 50 per cent. He believes the disease to be etiologically and clinically different from the usual form of infectious hepatitis. The cause is unknown. The mortality rate was 61 per cent in Jersild's patients.^{150a}

Other fulminant, fatal attacks of hepatitis of both the infectious and the homologous serum kind were described by Lucké and Mallory.¹⁵¹ The lesions at necropsy were the same in both kinds. By biopsy made by inserting a hollow needle into the liver in 8 patients with prolonged disease after an attack of viral hepatitis, Volwiler and Elliot¹⁵² found histologic evidence of persisting inflammatory changes. In 2 patients with severe hepatic impairment there were active inflammation and fibrosis. Havens and his co-workers¹⁵³ demonstrated acute inflammation

149. Tatlock, H.: Studies on a Virus From a Patient with Fort Bragg Fever (Pretibial Fever), *J. Clin. Investigation* **26**:287-297 (March) 1947.

150. Alsted, G.: Studies on Malignant Hepatitis, *Am. J. M. Sc.* **213**:257-267 (March) 1947.

150a. Jersild, M.: Infectious Hepatitis with Subacute Atrophy of the Liver: Epidemic in Women After the Menopause, *New England J. Med.* **237**:8 (July 3) 1947.

151. Lucké, B., and Mallory, T.: Fulminant Form of Epidemic Hepatitis, *Am. J. Path.* **22**:867-946 (Sept.) 1946.

152. Volwiler, W., and Elliot, J. A.: Late Manifestation of Epidemic Infectious Hepatitis, paper read before the American Society for Clinical Investigation, May 5, 1947.

153. Havens, W. P.; Kushlan, S. D., and Green, M. R.: Experimentally Induced Infectious Hepatitis: Roentgenographic and Gastroscopic Observations, *Arch. Int. Med.* **79**:457-464 (April) 1947.

Another fatal case of poliomyelitis in which the infection was apparently contracted in a laboratory was reported.¹³² As calculated, the probable attack rate among laboratory workers who handle poliomyelitis viruses or are exposed to them is 2 in 50 to 75. This is much higher than the attack rate in natural epidemics. Contact with freshly isolated strains is especially dangerous. In the case described infection apparently occurred through an injury to the skin of the arm, since virus was isolated from the lymph nodes draining the area and not from others.

Poliomyelitis virus is inactivated in the stomach at the hydrogen ion concentration which exists when only gastric juice is present and at the height of the digestive process.¹³³ When the acidity lessens, the virus passes through the stomach unharmed.

By a new method of inoculation with autolyzed brain tissue as an adjuvant, Milzer and Byrd¹³⁴ transmitted poliomyelitis virus directly from human feces and spinal cord to white mice. The virus may also be transmitted in this manner to other varieties of mice, to hamsters and to rhesus monkeys. The technic, if successful, will greatly simplify laboratory procedure for diagnosis, but according to reports other workers are having difficulty in repeating the method.

Poliomyelitis was thought to be uncommon in the tropics,¹³⁵ but as in the case of other supposedly uncommon conditions it is present and can be found if sought. Outbreaks are now recorded from many primitive areas.¹³⁶

Smallpox.—Thousands of cases of smallpox were reported from Asia and Africa in 1946.¹³⁷ During early spring, 8 cases occurred in New York city and a few others elsewhere, evidently traced to a traveler who caught the disease in Mexico. The outbreak caused great alarm, emphasized the danger of an explosive outbreak in persons who are not immune and led to the prompt vaccination of thousands of persons. There is considerable doubt if the duration of protection after vaccination lasts much more than six months.

132. Wenner, H. A., and Paul, J. H.: Fatal Infection with Poliomyelitis Virus in a Laboratory Technician: Isolation of Virus from Lymph Nodes, *Am. J. M. Sc.* **213**:9-18 (Jan.) 1947.

133. Faber, H. K., and Dong, L.: Inactivation of Poliomyelitis Virus in Relation to Gastric and Intestinal Digestion, *Proc. Soc. Exper. Biol. & Med.* **63**:575-578 (Dec.) 1946.

134. Milzer, A., and Byrd, C. L.: Autolyzed Brain Tissue as a Means of Facilitating Transfer of Experimental Poliomyelitis, *Science* **105**:70-72 (Jan. 17) 1947.

135. Sabin, A. B.: The Epidemiology of Poliomyelitis: Problems at Home and Among the Armed Forces Abroad, *J. A. M. A.* **134**:749-756 (June 28) 1947.

136. Dauer, C. C.: Incidence of Poliomyelitis in 1946, *Pub. Health Rep.* **62**:901-909 (June 20) 1947.

137. Foreign Reports, *Pub. Health Rep.* **62**:625 (April 25) 1947.

found during tuberculosis, relapsing fever, coccidioidomycosis, malaria and a variety of other diseases.

Lyon reports¹⁶¹ a case of "virus" myocarditis in infectious mononucleosis as recognized by electrocardiographic changes. The first demonstration of interstitial mononuclear cell myocarditis in mononucleosis was made by Allen and Kellner,¹⁵⁶ as stated on a previous page. Smadel and Warren¹⁶² reported on a "new" virus which caused encephalomyocarditis (E.M.C. virus) in a chimpanzee. Curiously, serum from 17 of 44 soldiers who had what was called "three day fever" in the Philippine Islands in 1946 neutralized the virus specifically, which suggested that the same virus caused their undiagnosed malady.

Reiter's Disease.—It is still uncertain if Reiter's disease is an entity caused by a virus or by pleuropneumonia-like organisms or if it is a sequel to bacillary dysentery. In one study¹⁶³ agglutinin for a strain of a pleuropneumonia-like organism was found in 4 female patients who had various combinations of colitis, arthritis, conjunctivitis, urethritis, cervicitis and lesions of the skin, 2 of whom had what was suggestive of Reiter's disease at it is reported in man. Agglutinin was not present in patients with urethritis or colitis without other involvement.

Dutch physicians point out,¹⁶⁴ as others have before, that a syndrome resembling Reiter's disease occasionally follows attacks of bacillary dysentery. When this occurs, the disease may last for months. Urethritis, polyarthritis and conjunctivitis may occur in sequence, separately or all at once. According to others,^{164a} Reiter's disease is always dysenteric in origin, yet in a study of 900 patients^{165b} only 3 had arthritis and in none were the eyes involved. In the present confusion with respect to Reiter's disease it may be better to regard it as a syndrome caused by a number of agents.

Abacterial Pyuria.—This puzzling condition, brought to attention by Wildbolz in 1933, is discussed in six papers.¹⁶⁵ Because bacteria

161. Virus Myocarditis, Foreign Letters, J. A. M. A. **133**:496 (Feb. 15) 1947.

162. Smadel, J. E., and Warren, J.: The Virus of Encephalomyocarditis and Its Apparent Causation of Disease in Man, abstracted, program of the American Society for Clinical Investigation, 1947, p. 31.

163. Wallerstein, R.; Vallee, B., and Turner, L.: Possible Relationship of Pleuropneumonia-Like Organisms to Reiter's Disease, Rheumatoid Arthritis and Ulcerative Colitis, J. Infect Dis. **79**:134-140 (Sept.-Oct.) 1946.

164. Koster, M. S., and Jansen, M. T.: Reiter's Disease, Nederl. tijdschr. v. geneesk. **90**:483-484 (May 18) 1946.

164a. Young, R. H., and McEwen, E. G.: Bacillary Dysentery as the Cause of Reiter's Syndrome (Arthritis with Nonspecific Urethritis and Conjunctivitis), J.A.M.A. **134**:1456-1459 (Aug. 23) 1947.

165. McGrim, E. J.: True Infective Abacterial Pyuria, Wisconsin M. J. **45**:845-847 (Sept.) 1946. Fieldsend, A. B.: Abacterial Pyuria Presenting as

A technic is described for the direct isolation of the virus of mumps in chick embryos.^{143a}

Herpes Simplex and Herpes Zoster.—Herpes virus may cause herpes simplex, stomatitis, pharyngitis, a varicelliform eruption, encephalomyelitis and keratitis. In 3 cases vulvovaginitis was caused by the virus.¹⁴⁴ A significant serologic difference between some of the strains indicates the existence of various types of herpes virus, as occurs among most infectious agents.

Herpes virus resided in the brain of a rabbit for nine months after it had been inoculated.¹⁴⁵ During this time attacks of encephalitis, presumably of herpetic origin, were precipitated by each of three induced anaphylactic reactions. This circumstance seems to be analogous to the presumed carrier state of herpes simplex virus in man. The virus apparently becomes invasive and pathogenic when provoked by other factors. Klauder¹⁴⁶ reports similar circumstances with herpes zoster. He describes 8 patients in whom the lesions appeared at the site of trauma after one to fourteen days and cites similar observations by others. Although a virus has never been proved to be the cause of herpes zoster, there is much in favor of the view, and to the extent discussed, the analogy to the behavior of herpes simplex as just mentioned is close.

In a patient with herpes zoster meningoencephalitis developed eight days after vaccination with vaccinia virus.¹⁴⁷ Presumably vaccine caused the agent of herpes zoster to invade the central nervous system, but perhaps it was vaccinia virus which invaded it.

Yellow Fever.—A major epidemic of yellow fever extending over 5,000 square miles (12,950 sq. kilometers) occurred in Nigeria in 1946.¹⁴⁸ It was the first known large outbreak of classic urban yellow fever transmitted by *Aedes aegypti* in fifteen years. The infection is

143a. Leymaster, G. R., and Ward, T. G.: Direct Isolation of Mumps Virus in Chick Embryos, *Proc. Soc. Exper. Biol. & Med.* **65**:346-348 (June) 1947.

144. Slavin, H. B., and Gavett, E.: Primary Herpetic Vulvovaginitis, *Proc. Soc. Exper. Biol. & Med.* **63**:343-345 (Nov.) 1946; Antigenic Dissimilarity Between Strains of Herpes Simplex Virus, *ibid.* **63**:345-347 (Nov.) 1946.

145. Good, R. A.: Recovery of Herpes Simplex Virus from Rabbit Brain Nine Months After Inoculation, *Proc. Soc. Exper. Biol. & Med.* **64**:360-362 (March) 1947.

146. Klauder, J. V.: Herpes Zoster Appearing After Trauma, *J. A. M. A.* **134**:245-248 (May 17) 1947.

147. Madonick, M. J.: Meningoencephalitis Complicating Herpes Zoster Ophthalmicus After Treatment by Vaccination, *Arch. Neurol. & Psychiat.* **56**:434-441 (Oct.) 1946.

148. Fosdick, R. B.: The Rockefeller Foundation: A Review for 1946, New York, 1947, p. 21.

explosive, and the mode of infection was not discovered. Cattle were suspected as the source. Of 136 persons exposed, 55 became sick and 2 died. Most of them had mild disease resembling influenza. Roentgenographic evidence of pulmonary involvement was present in most of the patients studied in the hospital.

Clinical studies show that 9 patients with Rocky Mountain spotted fever treated with paraaminobenzoic acid recovered in shorter time than those untreated.¹⁶⁹ Improvement seemed to begin shortly after the start of therapy. A level of 30 to 60 mg. per hundred cubic centimeters of blood is desired. Methylthionine chloride (methylene blue) was found to be superior to paraaminobenzoic acid in the treatment of experimental tsutsugamushi disease in mice.¹⁷⁰ Methylene blue had been reported to be of value in the treatment of typhus and other diseases by investigators ten or fifteen years ago. In other unpublished experimental studies (Smadel) a combination of streptomycin and paraaminobenzoic acid was more effective in experimental therapy of rickettsial diseases than either agent alone.

Gilliam¹⁷¹ reports some degree of protection against louse-borne typhus in Cairo after three doses of the Cox type vaccine. One or two doses were not satisfactory. According to Sadusk⁴ no deaths from typhus occurred in American soldiers between 1942 and 1945. In those years there were 64 cases of epidemic typhus, 603 cases of murine typhus and 6,685 cases of tsutsugamushi disease. The mildness of most attacks of epidemic typhus was ascribed to the use of antityphus vaccine. The author describes 5 cases of mild typhus in persons who had been supposedly adequately vaccinated. There is no evidence of the value of vaccine for the epidemic type of typhus as a prophylactic agent against murine typhus. Further report^{171a} on the treatment of typhus with paraaminobenzoic acid shows the results of therapy to shorten the disease and lower the mortality rate, but when mathematic methods must be used to show "statistical significance," the agent obviously is not as effective as it was hoped. The authors emphasize the importance of beginning treatment early, of keeping the amount in the blood over

169. Flinn, L. B.; Howard, J. W.; Todd, C. W., and Scott, E. G.: Para-Aminobenzoic Acid Treatment of Rocky Mountain Spotted Fever, *J. A. M. A.* **132**:911-915 (Dec. 14) 1946.

170. McLimans, W. F., and Grant, C. W.: Therapy of Experimental Tsutsugamushi Disease (Scrub Typhus), *Science* **105**:181-182 (Feb. 14) 1947.

171. Gilliam, A. G.: Efficacy of Cox-Type Vaccine in the Prevention of Naturally Acquired Louse-Borne Typhus Fever, *Am. J. Hyg.* **44**:401-410 (Nov.) 1946.

171a. Snyder, J. C., and others: Further Observations on the Treatment of Typhus Fever with Para-Aminobenzoic Acid, *Ann. Int. Med.* **27**:1-27 (July) 1947.

of the wall of the stomach (gastritis) reontgenographically and gastroscopically as one of the features of the acute stage of viral hepatitis. The condition may last into convalescence.

Studies on the prevention of hepatitis with immune globulin show that the immunity afforded against homologous serum jaundice is low as contrasted with that afforded against the infectious type.¹⁵⁴

Unconvincing report of the transmission of hepatitis to animals was published.¹⁵⁵ Duodenal fluid from patients was said to cause hepatitis in young pigs and white mice. Virus bodies were said to be seen in the duodenal fluid and in the hepatic lesion.

Mononucleosis and Lymphocytosis.—A patient convalescent from infectious mononucleosis was killed in an accident.¹⁵⁶ Necropsy studies revealed the disease to be a generalized one as reported by others previously. There were focal cellular infiltrations in the liver, kidneys, heart, lungs, adrenals, testes and brain. Lesions in the heart and brain are reported for the first time. These systemic involvements account for the variable clinical manifestations of the disease, which may simulate hepatitis, nephritis, myocarditis and viral pneumonia. Evidence of the placental transmission of infectious mononucleosis was observed.¹⁵⁷

Several more cases of acute infectious lymphocytosis were observed. A small outbreak of 6 cases occurred in England,¹⁵⁸ and 1 involving an adult was observed in this country.¹⁵⁹ The disease occurs chiefly in children and is benign but sometimes prolonged. Swelling of the lymph nodes, an exanthem and lymphocytosis are its characteristics.

Myocarditis.—In Gore's opinion¹⁶⁰ myocarditis occurs more often during acute infectious diseases than recent views indicate, particularly since the term myocarditis often is not used in its restricted sense to indicate actual inflammation. He presents evidence of myocarditis occurring during acute tonsillitis and nasopharyngitis and, as well known, in scarlet fever, diphtheria and meningococcemia. Myocarditis was also

154. Duncan, G. C., and others: An Evaluation of Immune Serum Globulin as a Prophylactic Agent Against Homologous Serum Hepatitis, *Am. J. M. Sc.* **213**:53-57 (Jan.) 1947.

155. Pendl, O.: Etiology of Contagious Hepatitis, *Wien. klin. Wchnschr.* **58**:669-672 (Nov. 8) 1946.

156. Allen, F. H., and Kellner, A.: Infectious Mononucleosis: An Autopsy Report, *Am. J. Path.* **23**:463-478 (May) 1947.

157. Trinção, C.: Infectious Mononucleosis in Puerperium, with Subclinical Infection of the Newborn Infant, *Lisboa méd.* **23**:146-152 (March) 1946.

158. Steigman, A. J.: Acute Infectious Lymphocytosis in England, *Lancet* **2**:944 (Dec. 28) 1946.

159. Yaskis, A. S.: Acute Infectious Lymphocytosis in an Adult, *J. A. M. A.* **132**:638-640 (Nov. 16) 1946.

160. Gore, I.: Myocarditis in Infectious Diseases, *Am. Practitioner* **1**:292-298 (Feb.) 1947.

toxic effects. In other studies¹⁷³ the synthetic drugs SN 6911 (3-methyl-4-[4-diethylamino-1-methylamino]-7-chloroquinidine), chloroquine and SN 8137 (4-[3-diethylamino-2-hydroxypropylamino]-7-chloroquinoline) were no more effective than quinacrine hydrochloride in controlling relapses of *P. vivax* malaria of foreign origin. Benign tertian malaria may develop more than a year after suppressive therapy is stopped.¹⁷⁴

In certain parts of Italy where engineering projects controlling swamps were destroyed during the war malaria is now over fifty times more common than in 1939.¹⁴⁸

A supplemental issue of the *American Journal of Tropical Medicine* for May deals with malaria in the South Pacific area.

Schistosomiasis.—Faust¹⁷⁵ reviews the literature on the subject of schistosomiasis and describes clinical studies on soldiers who contracted the disease in Leyte in the Philippines. Since the chronic form may appear in some of the victims long afterward, physicians should be aware of its signs and symptoms if they are encountered in men who have served in endemic areas.

Studies from Puerto Rico¹⁷⁶ show that the guppy (*Lebistes reticulatus*) feeds on egg masses laid by schistosome-bearing snails and on the cercarias shed by the snails. The guppy may be of importance in controlling these sources of *Schistosomiasis mansoni*.

Trichinosis.—Three epidemics of trichinosis were reported. The largest outbreak in New York city in years occurred in March 1945.¹⁷⁷ Eighty-four cases were recognized. Infection was caused by eating uncooked pork sausage. Edema of the eyelids, fever and eosinophilia were the commonest findings. Gastrointestinal symptoms were inconspicuous. The precipitin reaction, because of its earlier appearance, was more useful in diagnosis than the skin test.

An epidemic of trichinosis in mild form occurred in a prison camp.¹⁷⁸ Of 587 men, at least 139 were infected demonstrably, and 100 others were

173. Gordon, H. H.; Dieuaide, F. R.; Marble, A.; Christianson, H. B., and Dahl, L. K.: Treatment of *Plasmodium Vivax* Malaria of Foreign Origin: A Comparison of Various Drugs, *Arch. Int. Med.* **79**:365-380 (April) 1947.

174. Scheifley, C. H.: Malaria: A Note on Its Latency and Report of a Case, *Proc. Staff Meet., Mayo Clin.* **22**:49-52 (Feb. 5) 1947.

175. Faust, E. C.: *Schistosomiasis Japonica*: Its Clinical Development and Recognition, *Ann. Int. Med.* **25**:585-600 (Oct.) 1946.

176. Oliver-Gonzalez, J.: Possible Role of the Guppy, *Lebistes Reticulatus* on the Biological Control of *Schistosomiasis Mansoni*, *Letters to the Editor, Science* **105**:605 (Dec. 20) 1946.

177. Shookhoff, H. B.; Birnkrant, W. B., and Greenberg, M.: Outbreak of Trichinosis in New York City with Special Reference to Intradermal and Precipitin Tests, *Am. J. Pub. Health* **36**:1403-1411 (Dec.) 1946.

178. Hathaway, F. H., and Blaney, L.: Trichinosis: Report of an Epidemic, *Ann. Int. Med.* **26**:250-262 (Feb.) 1947.

to be related causally, some suspect the condition to cannot be proved to Others, impressed by reports of successful treatment be of viral origin. suspect a spirochete on that weak evidence alone. with arsphenamine, unimpressive as that favoring fusospirochetal micro- The evidence is as use of stomatitis. organisms as the ca

RICKETTSIAL DISEASES

In June 1946 a newly recognized rickettsial disease *Rickettsialpox*. several boroughs of New York city. It is a specific was discovered in spots other rickettsial diseases, and it is characterized entity which resembles on the skin at the site of infection, fever of short by a primary lesion, backache, headache, swelling of lymph nodes and a duration, sweats, etc. The causative agent is *Rickettsia akari*, which is vesiculopapular rash, transmitted by the rodent mite *Allodermmanyssus sanguineus*. conveyed from rodents isolated from naturally infected house mice in the The rickettsias were referred to the few papers on the subject are given in vicinity. Reference Heubner's ¹⁶⁷ reports. There is reason to believe Greenberg's ¹⁶⁶ and others elsewhere but has been unrecognized. that the disease exists

What may be a new form of "tick typhus" was alia. ¹⁶⁸ The disease was similar to but much milder reported from Australia. The disease (scrub typhus). An eschar occurs, and the than tsutsugamushi *Bacillus proteus* OX19 and not *B. proteus* OXK. serum agglutinates with that of scrub typhus imported by airplane is reported. ^{168a}

The first instance, clinical data, serologic observations and isolation

The epidemiology in an outbreak of Q fever among stock handlers in of *Rickettsia burnetii* described in four papers in the March 22 issue of Texas in 1946 was *American Medical Association*. The outbreak was *The Journal of the*

J. 2:439-494 (Oct. 5) 1946. Coutts, W. E., and Vargas- "Urethritis," *Brit. M. J.* 1 Pyuria with Special Reference to Infection by Spirochetes, Zalazar, R.: *Abacteriæ*. 28) 1946. Hamm, F. C.: Amicrobic Pyuria, *J. Urol. Lancet* 2:982-983 (Dec. 7. Baines, G. H.: Abacterial Pyuria from a New Angle, 57:226-232 (Feb.) 1947. Goldstein, A. E.: Reiter's Disease Followed *Brit. J. Urol.* 19:6-21 (March) 1947. *Abacteriæ*, *ibid.* 19:32-36 (March) 1947.

by True Infective Abacteriæ and Smyly, H. J.: Arthritis in Association with Bacillary 165b. Zia, S. H., and China 17:307-312, 1931.

Dysentery, *Nat. M. J.*; Pellitteri, O.; Klein, I. F., and Huebner, R. J.: Rickettsialpox—A Newly Recognized Rickettsial Disease: II. Clinical Observations, *J. A. Res.* 29) 1947.

M. A. 133:901-906 (March); Jellison, W. L., and Armstrong, C.: Rickettsialpox: 167. Huebner, R.: Rickettsial Disease, *Pub. Health Rep.* 62:777-780 (May 30) 1947.

Bonnin, J. M., and Williams, S.: Tick Typhus in North 168. Andrew, R.; *Australia* 2:253-258 (Aug. 24) 1946.

Queensland, M. J. A.: A Fatal Case of Scrub Typhus Introduced into the 168a. Dumanis, A.: *Int. Med.* 27:137-142 (July) 1947.

United States, *Ann. I.*

before or after birth. The disease is probably much more common than is generally believed and is often obscured by evidence of hydrocephalus, psychomotor disturbances, encephalitis, pneumonia and an exanthem.

A general review of toxoplasmosis was published.¹⁸⁵

Steves and Lynch¹⁸⁶ call attention to a generally unrecognized but alarmingly widespread epidemic of ringworm of the scalp. The infection has appeared apparently for the first time in many communities. It is resistant to treatment. A rare case of leptomeningitis caused by the fungus of corn smut is reported.¹⁸⁷

Wound Infections.—A series of papers in *The Journal of the American Medical Association* of January 25 deal with the problem of infected war wounds. Bacteria isolated from wounds are divided into three groups: A. The toxigenic and/or invasive ones are of greatest importance and can be controlled best by repeated surgical toilet of the wound and its closure. Locally applied chemotherapy is ineffective and deleterious. Penicillin given parenterally is the treatment of choice to supplement surgical treatment. If certain pathogens are highly resistant to penicillin, other agents are necessary. The only prophylactic procedure of value is the use of tetanus toxoid against tetanus. B. The proteolytic group of bacteria either alone or in symbiosis seem to cause septic decomposition of dead tissue and may become pathogenic. C. The group of commensals usually are saprophytic but may act synergistically with others and become invasive. Study of the problem is complicated and time-consuming because of the technic involved in anaerobic cultures and the slowness of growth of many varieties. The bacteria most frequently encountered were beta hemolytic streptococci, staphylococci, enteric streptococci, *Clostridium*, *Proteus*, *Pseudomonas* and coliform bacilli. Certain bacteria which are usually regarded as pathogenic may be present without becoming invasive.

Dienes¹⁸⁸ describes a different and more complex form of reproduction than the ordinarily recognized binary fission of gram-negative bacteria. Bacilli were seen to swell into large round bodies in which bacteria formed inside, or the swollen forms disintegrated into frag-

185. Callahan, W. P.; Russell, N., and Smith, M. G.: Human Toxoplasmosis, *Medicine* **25**:343-398 (Dec.) 1946.

186. Steves, R. J., and Lynch, F. W.: Ringworm of the Scalp: Report of Present Epidemic, *J.A.M.A.* **133**:306-309 (Feb. 1) 1947.

187. Moore, M.; Russell, W. D., and Sachs, E.: Chronic Leptomeningitis and Ependymitis Caused by *Ustilago*, Probably *U. Zeae* (Corn Smut): *Ustilagomycosis*; The Second Reported Instance of Infection, *Am. J. Path.* **22**:761-778 (July) 1946.

188. Dienes, L.: Reproductive Processes in *Proteus* Cultures, *Proc. Soc. Exper. Biol. & Med.* **63**:265-270 (Nov.) 1946.

10 mg. per hundred cubic centimeters for epidemic typhus and over 35 mg. for scrub typhus and of keeping the urine alkaline or neutral during treatment. Contraindications to therapy are crystals of para-aminobenzoic acid in the urine, a leukocyte count under 3,000 and a fall of the polymorphonuclear cells to below 25 per cent.

MISCELLANEOUS SUBJECTS

Malaria.—A summary of the advances in the knowledge of malaria gained chiefly during the war years was published by Sapero.¹⁷² Of importance is the information that the life cycle of certain plasmodia is not so simple as it seemed. A developmental cycle apart from the erythrocytic one apparently takes place in endothelial and tissue cells, in which the plasmodia of the vivax type are invulnerable to the well known antimalarial drugs. This fact probably explains the failure of quinine and quinacrine hydrochloride to cure the disease and to prevent relapses. There also have been shown to be variations in strains of *Plasmodium vivax* malaria to account for the striking clinical and therapeutic differences of the disease in the South Pacific as compared with malaria indigenous in the United States.

Presumed exoerythrocytic forms of malarial parasites in human blood and in tissue culture have been seen and described by several investigators.^{172a}

Quinine, quinacrine hydrochloride and chloroquine act principally on plasmodia in the erythrocytic phase and are suppressive whereas pamaquine, "paludrine," (N_1p -chlorophenyl- N_5 -isopropyl biguanide) and pentaquine act principally on the forms in the cells and tissue and are curative, especially in *P. vivax* malaria. *Plasmodium falciparum* malaria is more easily prevented and cured than other varieties with quinacrine or chloroquine. Great progress was made in the technic of epidemiologic control of malaria with preparations of the insecticide DDT. (4, 4'-dichlorodiphenyltrichloroethane). Repellents are of less value unless they are used under expert direction and thoroughness. Drug prophylaxis with quinacrine hydrochloride successfully prevents clinical attacks of malaria when applied according to prescription. Chloroquine is just as effective and does not discolor the skin; it can be given effectively as a weekly dose. "Paludrine" may prove to be superior. With coordination of efforts at entomologic control and drug therapy, malaria, like tuberculosis, could be eradicated from some areas in a generation.

I have observed a patient in whom chloroquine failed to control relapse of *P. vivax* malaria acquired in China and caused distressing

172. Sapero, J. J.: The Malaria Problem Today: Influence of Wartime Experience and Research, *J. A. M. A.* **132**:623-627 (Nov. 16) 1946.

172a. Dubin, I. N.: Bodies Suggesting Exoerythrocytic Forms of *Plasmodium Vivax* in Tissue Culture, *Proc. Soc. Exper. Biol. & Med.* **65**:154-156 (June) 1947.

bodies and gamma globulin. Previous studies by White and others had suggested a more important role of the adrenals in this respect.

Pappenheimer ^{191b} points out that there are only slight quantitative differences in the chemical composition of serum albumin and in some of the strongest poisons known, namely the toxins of diphtheria and botulinus bacilli. There is no clue as to why one protein is toxic and a similar one is not. The toxins of tetanus, diphtheria and botulinus bacilli have been crystallized within the past year.

191b. Pappenheimer, A. M.: Bacterial Toxins, *Federation Proc.* **6**:479-484 (June) 1947.

probably infected, as indicated by the presence of eosinophilia. The disease was at first mistaken for nasopharyngitis, sinusitis and malaria, but eosinophilia and swollen lids soon suggested the correct diagnosis. Fever, headache, malaise, muscular pain and swollen lids were the commonest symptoms. Diarrhea occurred in only 14 per cent. There was a similar but smaller outbreak in Sweden.¹⁷⁹ Some victims had muscular discomfort for eight months afterward.

Syverton and his co-workers¹⁸⁰ show that *Trichinella spiralis* is able to harbor the virus of lymphocytic choriomeningitis and to convey it when fed to animals. It is possible but unproved that this may be one of the natural modes of transmission of the viral disease, akin to Shope's demonstration of the existence of influenza virus in lung worms of swine.

Hookworm Disease.—Hookworm disease as a cause of death was described in 21 children of Guam.¹⁸¹ Terminal pulmonary infection often obscured the underlying disease. The chief lesions were acute jejunitis, with ulceration and necrosis, and peritonitis. Eosinophilic invasion was a prominent histologic feature.

Leptospirosis.—The first case of *Leptospira canicola* infection was recorded from England, involving a boy who bathed in the Thames.¹⁸² Diagnosis was made by the development in the serum of an agglutinin for the leptospira. Penicillin apparently was curative. Infection in another patient, most likely contracted from his sick dog, was diagnosed on clinical and serologic evidence.¹⁸³

Toxoplasmosis.—Adams, Horns and Eklund¹⁸⁴ studied a patient aged 14 with toxoplasmosis and investigated other members of the family as well. Positive reactions to the neutralization test were demonstrated with the blood of the patient's mother and with that of 8 of 9 siblings, none of whom were sick or had signs of disease. The results suggest that infection probably occurred subclinically or in unrecognized form in most members of the family and may have been acquired either

179. Wird, K.: Trichinosis Epidemic in Borås District, *Acta med. Scandinav.* **126**:1-16 (Oct. 15) 1946.

180. Syverton, J. T.; McCorry, O. R., and Koomen, J.: The Transmission of the Virus of Lymphocytic Choriomeningitis by *Trichinella Spiralis*, *J. Exper. Med.* **85**:759-769 (June) 1947.

181. Zimmerman, H. M.: Fatal Hookworm Disease in Infancy and Childhood on Guam, *Am. J. Path.* **22**:1081-1101 (Nov.) 1946.

182. Baber, M. D., and Stuart, P. D.: *Leptospirosis Canicola*: Case Treated with Penicillin, *Lancet* **2**:594-596 (Oct. 26) 1946.

183. Rosenbaum, H. D.: Canicola Fever: Case Report and Review of Literature, *Arch. Int. Med.* **78**:531-543 (Nov.) 1946.

184. Adams, F. H.; Horns, R., and Eklund, K.: Toxoplasmosis in a Large Minnesota Family, *J. Pediat.* **28**:165-171 (Feb.) 1946.

two describe the same idea in the same words, and their construction of sentences, punctuation and vocabulary differ widely. Yet they all demonstrate the basic values of brevity, clarity and unity in the art of writing.

The Physiological Basis of Medical Practice. By Charles Herbert Best and Norman Burke Taylor. A University of Toronto text in applied physiology. Fourth edition. Price, \$10. Pp. 1,169. Baltimore: Williams and Wilkins Company, 1945.

In this new (fourth) edition the authors have revised and enlarged on previous editions in order to present adequately the rapidly increasing advances in the field of physiology. It continues to be an excellent textbook of physiology from the conventional laboratory viewpoint. It does not, however, give the clinical viewpoint which the title suggests, nor does it afford the desired bridge from laboratory observation to clinical observation on patients or to therapy based on physiologic knowledge.

It is unfortunate that authors of textbooks of physiology do not more frequently have the clinical viewpoint and the knowledge of clinical problems and clinical literature which can come only from close contact with clinical problems and from carrying the responsibility of solving those problems. This is not a criticism, for no one man, even an "admirable Crichton," could possibly cover adequately the entire field of laboratory physiology and its application to the problems of clinical physiology daily met by the physician or surgeon. It might be done by one person covering only a limited section. It might be best to provide a separate course and separate text to serve as a bridge between classroom physiology and its bedside application. Aside from all this, "the physiological basis of medical practice" could possibly be more clearly demonstrated than it is in the text.

Peptic Ulcer: Its Diagnosis and Treatment. By I. W. Held, M.D., and A. Allen Goldbloom, M.D. Price, \$6.50. Pp. 382, with 110 illustrations. Springfield, Ill.: Charles C Thomas, 1946.

This is a business-like volume discussing from a variety of viewpoints not only peptic ulcers of the stomach and duodenum, with their varied complications, but also peptic ulcers of the esophagus and of Meckel's diverticulum and gastro-jejunal ulcers.

The contents are divided largely on the basis of the relative importance of the individual chapters. For example, the pathogenesis of ulcer is given considerable space, as is roentgenologic diagnosis, while physical findings and other laboratory procedures receive less attention; the pathology of ulcer is passed over quickly, while the treatment of hemorrhage is described in detail. The authors are internists and have prepared their book more for the benefit of fellow internists than for the benefit of surgeons; hence the technic of surgical procedures is given little emphasis. The methods of treatment which are advocated are described carefully and are based on common sense and experience.

The book is readable. It has a well chosen bibliography and a comprehensive index.

Familial Nonreaginic Food-Allergy. By Arthur F. Coca, M.D. Second edition. Price, \$3.75. Pp. 191. Springfield, Ill.: Charles C Thomas, Publisher, 1945.

The ARCHIVES (71:582 [April] 1943) reviewed the first edition of this book. The author believed that he had been able to assemble a group of cases of food allergy which differed in several respects from cases of atopic allergy. The method of recognition depended on the reaction of the patient's pulse rate to the administration of suspected antigens. The prediction was made that the book would be provoking but that its ideas would have to be confirmed before its concepts could be generally accepted.

ments which after a few divisions developed into regular bacteria or a variant form thereof.

Proteus bacilli may form colonies surrounded by a halo composed of filamentous forms which break into short rods and multiply as such. Large bodies attached to filaments may also form at the edges of certain opposing colonies. This suggests the participation in the formation of new forms of bacilli from the two adjacent colonies. The bodies may develop into regular bacilli or may produce the L type of growth. It is unlikely that the meeting of strains and the formation of peculiar forms represent a sexual process of multiplication.

Transformation of bacterial types is known to occur. Such changes had been suspected as accounting for the variability of the colon group of bacilli and have now been demonstrated.¹⁸⁹ By growth in special media, certain gram-negative bacilli were said to transform themselves into colon bacilli. The phenomenon of variation and transformation plays an important role in the resistance of bacterial strains to antibiotic agents as discussed earlier in this review. It also involves difficulties in the classification of bacteria by causing an instability of types hitherto regarded as fixed.

By electron photomicrography it was shown how the protoplasm of a single bacterial cell is transferred into sperm-shaped bacteriophage particles after the cell is invaded by one or more of them.¹⁹⁰

Diet.—Schneider¹⁹¹ points out the variable conditions which must be considered in studies of natural resistance as they pertain to the host and to its potentially invasive bacteria. For statistical studies, contrary to general opinion, the test hosts must not be genetically homozygous and the population of the infecting pathogens must not be uniform but must contain a number of variant forms such as may be expected under natural conditions. In experiments using mice of mixed genetic source and unselected cultures of *Salmonella typhi murium*, nutritional factors as supplied by selected diets significantly enhanced resistance.

Eisen and his co-workers^{191a} were unable to show that adrenal cortical activity has more than a transient effect on the formation of anti-

189. Poe, C. F., and Tregoning, J. J.: Bacterial Variation in Salicin Medium, *Proc. Soc. Exper. Biol. & Med.* **63**:561-562 (Dec.) 1946.

190. Edwards, O. F., and Wyckoff, R. W. G.: Electron Micrographs of Bacterial Cultures Infected with Bacteriophage, *Proc. Soc. Exper. Biol. & Med.* **64**:16-19 (Jan.) 1947.

191. Schneider, H. A.: Nutrition of the Host and Natural Resistance to Infection, *J. Exper. Med.* **64**:305-322 (Oct.) 1946.

191a. Eisen, H. N., and others: Failure of Adrenal Cortical Activity to Influence Circulatory Antibodies and Gamma Globulin, *Proc. Soc. Exper. Biol. & Med.* **65**:301-306 (June) 1947.

have attributed the excess absenteeism because of sickness to poorer nutritional habits on the part of women. Industrial injuries causing disabilities of one day or longer accounted for less than 1 per cent of all disabilities among female employees, and there is no reliable evidence to support the generally accepted view that women are more susceptible than men to occupational diseases.

It is obvious that pregnancy places a definite limit on a woman's ability to do physical work, but there is no reason why a pregnant woman should not continue certain types of work if they are properly controlled and if the industrial physician supervises her placement. Employed women have fewer children than others, but this does not of necessity imply that the low fertility among them results from employment. It more probably indicates merely that women who do not have children enter industry more frequently than do those with children.

The book is fully documented and undoubtedly will prove useful to physicians in and out of industry as well as to managers of personnel departments.

The Diagnostic and Prognostic Meaning of the Demonstration of Tubercle Bacilli in Gastric Lavage in Adults. By Oli Hjalsted. Copenhagen, Denmark: Ejnar Munksgaards Forlag, 1941.

The work demonstrates the unmistakable value of gastric lavage in the diagnosis of pulmonary tuberculosis in adults. An attempt was also made to see if the method had any prognostic implications, but without success. At least more can be determined by repeated roentgenologic study, in which the trends in the character of the lesions can be followed. Patients having gastric washings negative for tubercle bacilli frequently became worse, while as many patients having material which was positive for the organisms improved. There is no doubt that the stage of evolution of the disease had more to do with prognosis than the presence or absence of bacilli.

The records of the controls, including those who gave positive and those who gave negative reactions for tubercle bacilli, were thoroughly studied and documented. The author has confirmed the established fact that tubercle bacilli are not found in persons with no evidence of disease in the lungs even though they may work around infected persons.

The material proper was divided into three groups (exclusive of controls) as follows:

- (1) Patients with "hazy" pulmonary fields but without infiltrations.
- (2) Patients with pleurisy, who were subdivided into patients with and without visible infiltrations.
- (3) Patients with definite parenchymal infiltrations, who were subdivided into patients without visible cavitation, those with doubtful cavitation and those with definite cavitation.

The patients without any visible cavitation (making up most of the group) were divided into fifteen subgroups according to the lung and lobe involved, the degree and character of lesions and the involvement of the hilus.

Exclusive of the controls and the nontuberculous patients, there were 577 "negative" patients, of whom the author found 211 had tubercle bacilli, or 36.5 per cent. The figure is lower than the 48.7 per cent found by Stadnichenko, Cohen and Sweany (published one year earlier, *J. A. M. A.* **114**:634-639 [Feb.] 1940). In their almost identical series of 511 cases there were 249 patients who harbored tubercle bacilli (nearly 25 per cent of those giving positive reactions).

For material so much alike, the difference of 12.2 per cent is considerable. The cause may be due to the delay of twenty-four or more hours in the transfer of the material to the Serum Institute for culture. Sprick and Towey (*Pub. Health Rep.* **61**:648, 1946) obtained 39 per cent poorer results by allowing specimens to stand at room temperature twenty-four hours before neutralizing than by working the specimen up at once. In forty-eight hours their results were 67 per cent worse. Storage of the specimens in ice boxes in the intervening time no doubt prevented much spoilage, but the delay in working up the material seems to have vitiated the authors' otherwise good work.

Book Reviews

Diagnosis in Sterility. Edited by Earl T. Engle. Conference on Problems in Human Fertility, Sponsored by the National Committee on Maternal Health, January 26-27, 1945, New York. Price, \$5. Pp. 248, with 63 illustrations. Springfield, Ill.: Charles C Thomas, 1946.

Dr. Harvey Cushing once remarked that the chief justification for the specialist was his ability to do research; he should explore new fields in medicine, always striving to make the results of his explorations promptly useful to men in general practice. To those interested in the broad aspects of internal medicine this viewpoint is sound.

The management of sterility is not a new specialty. Every internist in the course of his work encounters couples who are baffled by their apparent inability to have children. A group of physicians, including pathologists and biochemists as well as clinicians, have become sufficiently aware of this to form a society under the auspices of the National Committee on Maternal Health. This volume presents the record of the first meeting.

It makes a readable book, describing how the problems of sterility can now be scientifically attacked, the methods currently used, such as semen analysis and testicular or endometrial biopsy and the proper type of history to be taken in studying the infertile couple. It ends with a general summary by Dr. John Rock, of Boston. Dr. Rock's concluding sentence emphasizes the continued need for common sense in dealing with a clinical matter in which emotion may often play an essential part. As he says, functional defects in the reproductive apparatus are not recognizable by most of the objective tests, and it is only in function that the reproductive organs can be judged.

Research and Regional Welfare. Papers Presented at a Conference on Research at Chapel Hill, May 9-11, 1945. (University of North Carolina Sesquicentennial Publications.) Edited by Robert E. Coker. Price, \$3. Pp. 229. Chapel Hill, N. C.: University of North Carolina Press, 1946.

When the University of North Carolina celebrated its sesquicentennial, it held, among other events, a three day conference on research. The Concise Oxford Dictionary defines the word as meaning an endeavor to discover facts by scientific study of a subject. Evidently the planners of the conference accepted an equally broad definition, and thus their program included a group of addresses by eminent speakers who were interested in the development of knowledge in a variety of different fields.

The addresses are printed in this book. In general, they point to research as the key to the future; they emphasize particularly, however, the importance to the South of research in nutrition and public health, in the humanities and social sciences, in the physical sciences and industry and in the biologic sciences.

The volume makes a valuable collection; certainly it should find a place in every library. Physicians are likely to read with particular care Dr. R. M. Wilder's paper on the importance to public health of research in nutrition, General J. S. Simmon's paper on the foundation for progress in health and public welfare in the South and Mr. D. E. Lilienthal's paper on the moral responsibility of research.

Those who have any special concern with the use of the English language will find the book unusually stimulating. Each contributor is a man of distinction. Even an amateur student of literature will be struck by the differences in literary style adopted by a state governor, a university president, a professor of English, a professor of history, a professor of medicine and a national figure in industry. No

his associates, a full and intensively documented account of the development of the subject is given. The thoroughness of the discussion can be inferred from the bibliography of over twelve hundred references! The experimental work on hypertension and the clinical implications are reviewed. There are numerous charts, tables, diagrams and graphs illustrating the text, and the format of the book and the large type are attractive. Dr. Dexter is to be congratulated on his excellent translation and thanked by English-speaking readers for bringing within their scope this admirable monograph.

Peripheral Vascular Diseases. By Edgar V. Allen, Nelson W. Barker and Edgar A. Hines Jr. Price, \$10. Pp. 871, with 386 illustrations. Philadelphia: W. B. Saunders Company, 1946.

As a whole, this monograph is good. The authors attempted to cover the field of vascular diseases with completeness, but like all single volume monographs on such an extensive subject, the book fails to be complete. The approach to the problem is, as would be expected, a good version of the approach to the various problems at the Mayo Clinic. For that reason, many differences of opinion which originate elsewhere are not completely considered. The authors have failed to assay adequately the many therapeutic, diagnostic and mechanistic approaches to and opinions of the vascular diseases for the physician who is little acquainted with the problems. In their attempt to make the monograph encyclopedic, they present many ideas without fully evaluating or summarizing the problems for the physicians and students who are unable to do so. A number of methods of diagnosis and treatment presented are useless, but known to be valueless by only the experienced clinicians. As in any book, there are certain errors which have crept in. On page 742, for instance, appears the statement that cold does not depress transmission of nerve impulses, and on page 747 (fig. 327) an elastic bandage is shown held in place by a nondistensible cotton tape, which must obstruct venous return if it supports the bandage. Such errors, however, are obvious and the result of carelessness. As a whole, the monograph is good and should prove to be of value to physicians and students concerned with vascular diseases.

Pneumoperitoneum Treatment. By Andrew L. Banyai, M.D. Price, \$6.50. Pp. 376, with 74 illustrations. St. Louis: The C. V. Mosby Company, 1946.

Not many years ago, medical students were taught that patients with peritoneal tuberculosis were often remarkably improved when air was placed within the peritoneal cavity. After a time this form of treatment passed into disuse, and pneumothorax or some form of collapse therapy for pulmonary tuberculosis and other intrathoracic diseases came to the front. Now, perhaps, the pendulum is swinging the other way; at least, here is a book describing the therapeutic value of the former approach.

Its contents are divided into two parts: The first deals with basic principles and the second with therapeutic application.

The first part gives an excellent account of the history of pneumoperitoneum and deals with technic and with the changes in physiology induced by the artificial introduction of air into the abdominal cavity. One gathers that in the hands of an expert the intraperitoneal injection of air is not difficult and that serious complications, such as air embolism or mediastinal emphysema, are rare.

The second part describes the various diseases in which pneumoperitoneum may be used therapeutically. These range from tuberculosis within the abdominal cavity to conditions within the chest; in fact, pulmonary tuberculosis, abscess of the lung, bronchiectasis and even bronchial asthma have on occasion seemed to prove amenable to such treatment.

The concluding chapter is one of bibliography. There are many titles listed, more from foreign than from domestic literature and predominantly old rather than new.

The second edition is a revision of the first. With engaging frankness, the author confesses that his earlier work was greeted by his colleagues with unpromising skepticism. He feels, however, that an interest in the subject is now stirring, and this has led him to the second publication.

His ideas continue to need confirmation.

Unlike most new editions, the present one is \$1.25 less expensive than its predecessor in spite of its twenty-five page growth in length.

A Future for Preventive Medicine. By Edward J. Stieglitz. Studies of the New York Academy of Medicine, Committee on Medicine and the Changing Order. Price, \$1. Pp. 77. New York: Commonwealth Fund, 1945.

This small volume was printed under the auspices of the Commonwealth Fund. It contains a lecture delivered at the New York Academy of Medicine as part of a series on the general topic of medicine in the future. Evidently it was prepared for public consumption and thus is written in simple, nontechnical language. It makes pleasant reading.

The changes in public health which have taken place in the last forty years are emphasized by simply constructed tables, and the hazards to the health of an aging population are duly stressed. Looking to the future, the author gives chief emphasis to the value of research and education to public health. He believes that good health can be given to no one; it is the task of the individual to earn it, and his ability to do this will depend to an increasing degree on his intelligence, energy and desire as means for preventing disease are further developed.

Every publication of the Commonwealth Fund is attractively printed and well indexed. This monograph is no exception.

Women in Industry: Their Health and Efficiency. By Anna M. Baetjer, Sc.D. Issued under the auspices of the Division of Medical Sciences and the Division of Engineering and Industrial Research of the National Research Council. Prepared in the Army Industrial Hygiene Laboratory. Price, \$4. Pp. 344. Philadelphia: W. B. Saunders Company, 1946.

This monograph is a critical review of information on the suitability of women for employment. In certain months of 1944 and 1945, 18,000,000 women were employed, more than one third of the total female population 14 years of age or more of the United States. Many of these women performed types of work which heretofore have been considered suitable only for men. This has focused attention on problems which arise not only because of physiologic processes peculiar to women but because of differences between men and women in social background and extra-employment responsibilities. Recent trends suggest that the number of women gainfully employed will continue to be larger than it was before the war, and the data here provided should assist in the formation of policies for the employment of women. It also is expected that the book will stimulate research and the collection of statistics greatly needed in this field.

Of special interest to the reviewer were the following observations: Women fatigue more rapidly than men, probably largely because of household duties and responsibilities which require many hours of work outside those spent in industry. Most authorities recommend a maximum of forty-eight working hours for employed women and restriction of working time to six hours per day in the case of those who have the care of children or sick or aged persons. Rest periods appear to be advantageous, and an adequate luncheon period is essential. Equal pay and equal opportunity for advancement in comparison with those for men are essential in obtaining maximal output. The mortality rate for men of every age is higher than it is for women. Women are ill more frequently and lose more time from work because of sickness. However, their absences are shorter in duration. The reason for the excess absenteeism due to sickness among women as compared with men is not entirely clear. The excess sickness is not limited to diseases related to sexual functions but occurs for diseases common to both sexes. Some persons



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PERIARTERITIS NODOSA

A Report of Two Cases, One with Special Reference to Sensitivity Factors

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BOSTON

AN ENORMOUS amount of medical literature has been published on the subject of periarteritis nodosa since the disease was first described by Kussmaul and Maier in 1865.¹ Many authors have made a systematic study of the literature and of the disease, the most complete being the articles by Dr. Linn J. Boyd,² of the New York Medical College, who wrote an excellent series of eight papers during the years 1938 to 1944.

Within recent years an etiologic agent has been suspected by several investigators. In 1936 Cohen and others³ reported 2 cases in which the disease was associated with a definite family history of allergy and in which allergic manifestations preceded the onset. They stated in this report: "Our experience with this condition has led us to the conclusion that it is a manifestation of clinical allergy of so severe a degree that irreversible and destructive lesions appear in the blood vessels and lead to disturbances in the function of the organs supplied by the involved vessels." Rackemann and Greene⁴ pointed to the presence of asthma in

From the departments of hygiene and medicine, Harvard University, and the Medical Clinic of the Peter Bent Brigham Hospital.

1. Kussmaul, A., and Maier, R.: Ueber eine bisher nicht beschriebene eigenthümliche Arterienkrankung (Periarteritis nodosa), die mit Morbue Brighti und rapid fortschreitender allgemeiner Muskellähmung einhergeht, *Deutsches Arch. f. klin. Med.* **1**:484, 1865.

2. Boyd, L. J.: I. The Clinical Aspects of Periarteritis Nodosa, *Bull. New York M. Coll., Flower & Fifth Ave. Hosps.* **1**:219 (Dec.) 1939; II. The Clinical Aspects of Periarteritis Nodosa, *ibid.* **3**:32 (April) 1940; III. Periarteritis Nodosa: Cutaneous Symptoms, *ibid.* **3**:175 (Oct.) 1940; IV. Periarteritis Nodosa: Neuromyositic Manifestations, *ibid.* **3**:272 (Dec.) 1940; V. Periarteritis Nodosa: Abdominal Manifestations, *ibid.* **4**:27 (April) 1941; VI. The Renal and Cardiac Manifestations of Periarteritis Nodosa, *ibid.* **4**:176 (Dec.) 1941; VII. The Cerebral and Ocular Manifestations of Periarteritis Nodosa, *ibid.* **6**:130 (Oct.) 1943; VIII. Pulmonary Manifestations of Periarteritis Nodosa, *ibid.* **7**:94 (Oct.-Dec.) 1944.

3. Cohen, M. B.; Kline, B. S., and Young, A. M.: The Clinical Diagnosis of Periarteritis Nodosa, *J. A. M. A.* **107**:1555 (Nov. 7) 1936.

4. Rackemann, F. M., and Greene, J. E.: Periarteritis Nodosa and Asthma, *Tr. A. Am. Physicians* **54**:112, 1939.

It is always difficult to say when and under what conditions the last living tubercle bacillus will die in any specimen or when the last living tubercle bacillus has been grown by any given method of culture. Perhaps the best method today will be improved on tomorrow. When fresh material is used on animals, however, the error is never great.

A final word should also be said regarding the possibility of the presence of avirulent saprophytes in gastric washings. They are not common, but they occur sufficiently often to indicate that a test for virulence should be done on all atypical cultures of acid-fast bacilli found in the sediment obtained by gastric lavage.

Barring a few minor imperfections, the work is to be highly commended, not only because it is complete but because it places deserved emphasis on gastric lavage as a means of diagnosis in pulmonary tuberculosis.

Diseases of the Digestive System. Edited by Sidney A. Portis, M.D., F.A.C.P. Second edition. Price, \$11. Pp. 932, with 182 illustrations. Philadelphia: Lea & Febiger, 1944.

It is good to see a second edition of this valuable book to which so many able men have contributed. One wishes for time in which to read it from cover to cover because the many chapters are so full of thought-producing ideas. Every young man who aspires to be a gastroenterologist will do well to read and reread this book. It is particularly valuable because the chapters have been written by men much interested in the subject assigned to each. Today no one, no matter how erudite, could hope to cover the whole field well or authoritatively. There has been so great an increase in knowledge that no one can hope to keep up with the literature even of a specialty such as gastroenterology. Because of this, every research worker, teacher and leader must, to a large extent, specialize within his specialty.

It is good to note fine chapters on the anatomy and physiology of the several sections of the digestive tract and also several chapters on the nervous and psychic influences which upset digestion.

The chapter on allergy leaves much to be desired because the author clings to the now well discredited idea that skin tests are of decided value in finding the offending foods and only mentions Rowe's elimination diets. He does not even mention the probably much more helpful diary method. In later editions of the book this serious defect should be remedied. Unfortunately, few of the allergists, whose main concern is the treatment of hay fever and asthma, seem to have made any intelligent effort to grapple with the problems of sensitiveness to foods.

Older gastroenterologists who, in all their years of talking intimately to nervous and psychopathic patients, have never heard one of them speak of the weird ideas of oral receptions and rectal giving that so dominate the writings of Dr. Alexander may experience considerable anorexia and regurgitation when they come to his chapter. They will also wonder how often one really cures a psychopathic patient in whom the disease is hereditary when one listens by the hour to his bizarre ideas. Like the famous author of *The Locomotive God*, he is likely to be still psychotic after he has had his mental catharsis.

But these wonderings of a pessimist and a doubting Thomas must not be allowed to obscure for a moment the delight over this volume and the admiration for the skill with which, in these extremely busy war years, Dr. Portis got so much good work out of so many good men.

Renal Hypertension. By Eduardo Braun-Menendez, Juan Carlos Fasciolo, Luis F. Leloir, Juan M. Munoz and Alberto C. Taquini. Translated by Lewis Dexter, M.D. Price, \$6.75. Pp. 483, with 107 illustrations. Springfield, Ill.: Charles C Thomas, 1946.

Few names, if any, are more outstanding in the modern study of hypertension than those of the group who have worked in the Institute of Professor Houssay in Buenos Aires. In this monograph under the authorship of Braun-Menendez and

and that in 1937 Clark and Kaplan¹¹ had described 2 cases of lobar pneumonia in which serum sickness developed shortly before death after treatment with serum. In these cases lesions of periarteritis nodosa were present at autopsy. Reimann¹² reported 2 cases in which the patients had trichinosis, and he suggested a relationship to the high degree of anaphylactic reaction to the trichina antigen.

Moschcowitz,¹³ in a recent and impressive essay on the biology of periarteritis nodosa, called attention to the reports of Masugi and his co-workers,¹⁴ who produced both glomerulonephritis and periarteritis nodosa in animals sensitized to egg white by injecting the antigen into the general circulation and directly into the renal vein.

In his book, "Essentials of Clinical Allergy," Taub¹⁵ wrote, in reference to periarteritis nodosa: "It is very likely that this disease is a manifestation of a hypersensitivity similar to drug allergy, serum sickness, or bacterial allergy with the allergic response occurring in the blood vessel walls as a result of the union of antigen and reagin in these tissues." This author found that a high blood eosinophil content is usually present, as evidenced by the 2 cases which he reports, in 1 of which it reached 60 per cent and in the other 70 per cent.

With this concept of the etiologic factor in the causation of periarteritis nodosa, 2 cases are presented, 1 of which is believed to demonstrate the hypersensitivity of a person to a condition heretofore not specifically stated, namely cervical glandular tuberculosis. The difficulty in diagnosis, the clinical course and the prognosis for this patient who is now alive and well have been most unusual. The second patient, in whom the course of the disease contrasted markedly to that in the first and in whom no specific etiologic factor could be demonstrated, died suddenly.

CASE 1.—F. C., with quiescent periarteritis nodosa, is a Chinese who at the time of the writing of this paper is alive and well at the age of 40 and teaching in Canton, China, as associate professor of chemistry at the University of Canton.

He was born in San Francisco. His mother died of a "heart attack" at the age of 50, but his father and four brothers and four sisters are living and well. There was no history of tuberculosis, diabetes, cancer, allergy, epilepsy, insanity or

11. Clark, E., and Kaplan, B. I.: Endocardial, Arterial, and Other Mesenchymal Alterations Associated with Serum Disease in Man, *Arch. Path.* **24**:458 (Oct.) 1937.

12. Reimann, H. A.; Price, A. H., and Herbut, P. A.: Trichinosis and Periarteritis Nodosa: Differential Diagnosis; Possible Relationship, *J. A. M. A.* **122**:274 (May 29) 1943.

13. Moschcowitz, E.: Essays on the Biology of Disease: Periarteritis Nodosa, *J. Mt. Sinai Hosp.* **12**:1054 (March-April) 1946.

14. Masugi, M., and Isibasi, T.: Ueber allergische Vorgänge bei Allgemeininfektion vom Standpunkt der experimentellen Forschung, *Beitr. z. path. Anat. u. z. allg. Path.* **96**:391, 1936. Masugi, M., and Sato, Y.: Ueber die allergische Gewebsreaktion der Niere, *Virchows Arch. f. path. Anat.* **293**:615, 1934.

15. Taub, S. J.: *Essentials of Clinical Allergy*, Baltimore, Williams & Wilkins Company, 1945, pp. 168-169.

The book is interesting because it is well written and is a sincere piece of work. The author evidently believes in the value of this particular method of treatment for a variety of unrelated disorders and states his views honestly, and thus has assembled a useful textbook, informative as well as helpful for reference.

Die spezielle Pathologie und die Verletzungen der Mundgebilde. By Anton Fonio. Price, 12.80 Swiss francs. Pp. 200, with 12 illustrations. Bern: Verlag Hans Huber, 1945.

This is an interesting book, written by the professor of surgery at the University of Bern (Switzerland). It discusses diseases of the oral cavity, including those of the teeth, tongue, lips, cheeks and tonsils. Little reference is made to work in this territory accomplished on this side of the Atlantic, so that, on the whole, the volume portrays only the European viewpoint toward oral medicine.

The contents are planned logically and deal with many topics on the borderline between dentistry and medicine. One of the book's most engaging features is that no differentiation is made between dentistry and medicine or surgery, the underlying purpose being to discuss the diagnosis and treatment of diseases of the oral cavity whether the latter be by diet, drugs, hygiene or mechanical means. One gets the impression that oral medicine is expanding rapidly abroad and that cooperative effort between dentists, physicians, surgeons and oral hygienists is accomplishing a great deal.

A Primer for Diabetic Patients. By Russell M. Wilder, M.D. Eighth edition. Price, \$1.75. Pp. 192, with 8 illustrations. Philadelphia: W. B. Saunders Company, 1946.

Anything of Dr. Wilder's requires no recommendation, and indeed this primer for diabetic patients is known to all as a valuable guide. The most noteworthy addition in this edition is the remarks on the use of mixed insulins. The book should be equally useful for patient and physician.

The American Hospital. By E. H. Lewinsky-Corwin. Studies of the New York Academy of Medicine, Committee on Medicine and the Changing Order. Price, \$1.50. Pp. 226. New York: Commonwealth Fund, 1946.

This handsomely printed little monograph keeps up well with the standards of book-making set by the Commonwealth Fund. Sponsored by the Committee on Medicine and Changing Order of the New York Academy of Medicine, the object of this publication is to give a concise, factual summary concerning American hospitals. This is well done in chapters on the development of hospitals and in presentation of data on size, distribution, operating costs, house staff and other factors. There are comprehensive lists of references at the end of each chapter. The book, on the whole, is written from the standpoint of the technical expert and unfortunately deals only in a limited way with some of the most important problems of medicine. The author does not clearly show the fundamental difference of purpose between the university teaching hospital and other hospitals. In his discussion of house staff he does not definitely point out the vital difference between training select men to be future teachers and investigators in medicine and merely preparing physicians in a routine way to qualify for the so-called specialty boards. Too much emphasis is placed on the authority of the specialty boards and other appraising organizations, which after all, with the best intentions, have centered attention on standardization rather than on development of the outstanding few on whom the entire future of medicine depends.

periarteritis nodosa. The white blood cell count on June 12 was 13,500, and the urine was normal.

On June 19, 1941, the patient was transferred to the Peter Bent Brigham Hospital, where he remained for six days. During his stay there, his temperature continued to be elevated although never exceeding 101 F. The physical condition remained as before. When he was discharged from the Peter Bent Brigham Hospital, the diagnosis was as follows: pulmonary tuberculosis (inactive), tuberculosis of cervical lymph nodes and periarteritis nodosa. The prognosis was considered decidedly unfavorable, and he was advised to return to his home in California for complete rest. He carefully followed the advice given to him and spent three months in a sanatorium, with a continued slow improvement in his health. At the end of this time he was discharged feeling well. He returned to Harvard University and continued his work as a research chemist, remaining well, with some weight increase, until July 28, 1942, when he was seen again at the Infirmary with his usual symptoms. His temperature was 100 F. and his throat moderately red, and at the temporomandibular angle at the left side of the neck there was a node the size of an almond, easily palpable. He remained in the Infirmary for five days, during which time his temperature came down to normal and the swelling in his neck subsided. He was symptom free for only three days after his discharge, and on Aug. 5, 1942, he was readmitted with the same complaints as previously—fever, sore throat and general malaise. His temperature was 101 F., and for the next thirty days it remained elevated, although never going any higher. There were several easily palpable cervical glands. His sedimentation rate was markedly increased, as usual. On August 18 his white blood cell count was 12,300 and the urine was normal. At one time during this period there was the questionable appearance of small nodes in the left arm, which were not large enough for biopsy. At this time the patient complained of aches and pains in the legs, which were not severe in nature but which persisted for one week. He remained in the Infirmary until Oct. 1, 1942, at which time he returned to his duties as a chemist and carried on fulltime activities with the exception of a short period of hospitalization in April 1943 for a perianal abscess. Although the diagnosis was periarteritis nodosa when he was discharged from the Infirmary in October 1942, there was no evidence of a wasting or chronic disease manifested either by symptoms or by physical signs. The sedimentation rate, however, continued to be increased to about three times normal.

On April 28, 1944, the patient was again admitted to the Infirmary with a recurrence of the symptoms for which he had been hospitalized so many times before. At this time his temperature was 101 F., the urine and blood counts were normal and a roentgenogram of his chest showed no change. Several days later enlargement of the posterior cervical lymph nodes developed on the right side of his neck. He again complained of aches and pains in his legs, and loss of weight was conspicuous. On May 9, 1944, he was transferred to the Peter Bent Brigham Hospital for further study. He continued to have fever, and the nodes in his neck became larger than at any time during his illness. Nodes the size of buckshot again developed under the skin of the left arm, one of which was excised and revealed active periarteritis nodosa. A node from the right side of the neck was also excised, and biopsy showed active tuberculosis. The finding of active tuberculosis in a patient with periarteritis nodosa was of the utmost importance and interest and will be discussed later. Throughout his stay at the Peter Bent Brigham Hospital (until July 3, 1944, when he was transferred to Stillman Infirmary for convalescence) he had low grade fever, the temperature ranging in general between 99 and 100 F. in the evening. Malaise slowly decreased, but the nodes in his neck remained tender and swollen. About three weeks after his admission to the hospital, he began to note transitory vague

cases of periarteritis nodosa, as did also Wilson and Alexander,⁵ who found that bronchial asthma antedated periarteritis nodosa in almost every instance in the 18 per cent of 300 cases of asthma which they studied.

It is a temptation to discuss in detail the interesting and numerous papers of recent years in which the sulfonamide compounds are suspected of being an inciting factor in the disease. One of interest was published in the *Lancet* in 1945 by Rosenak and Maschmeyer.⁶ Of special interest, however, is work done by Rich in Baltimore at the Johns Hopkins Hospital. In 1942, he stated⁷:

Vascular lesions characteristic of periarteritis nodosa have been found in the viscera of five patients who, shortly before death, had had hypersensitive reactions following therapeutic injections of foreign serum. Four of these patients had received sulfonamides, but in at least two of those cases the evidence indicates that the hypersensitive reaction was serum sickness and not drug hypersensitivity.

In February 1943 Rich⁸ stated that typical diffuse periarteritis nodosa had been produced experimentally by establishing in rats a condition analogous to serum sickness in man and that these experiments demonstrate that periarteritis nodosa is one manifestation of the anaphylactic type of sensitivity. In 1945 the same author reported evidence that hypersensitivity to chemicals other than foreign serum or sulfonamide compounds has been demonstrated.⁹ A patient with hyperthyroidism was being treated with iodine at the Johns Hopkins Hospital. A severe hypersensitive reaction developed with fever and considerable dermatitis. After a short, stormy course, the patient died, and at autopsy infiltrations of mononuclear cells and eosinophils were observed in various organs and also many fresh lesions of periarteritis nodosa. In this same article Rich recalls that twenty years before, Gruber¹⁰ had suggested that periarteritis nodosa might be the result of hypersensitivity

5. Wilson, K. S., and Alexander, H. L.: The Relation of Periarteritis Nodosa to Bronchial Asthma and Other Forms of Human Hypersensitivity, *J. Lab. & Clin. Med.* **30**:195 (March) 1945.

6. Rosenak, B. D., and Maschmeyer, R. H.: Periarteritis Nodosa, Possibly Due to Sulphadiazine Sensitivity, *Lancet* **1**:305 (March 10) 1945.

7. Rich, A. R.: The Role of Hypersensitivity in Periarteritis Nodosa as Indicated by Seven Cases Developing During Serum Sickness and Sulfonamide Therapy, *Bull. Johns Hopkins Hosp.* **71**:123 (Sept.) 1942.

8. Rich, A. R., and Gregory, J. E.: Experimental Demonstration That Periarteritis Nodosa Is a Manifestation of Hypersensitivity, *ibid.* **72**:65 (Feb.) 1943.

9. Rich, A. R.: The Role of Hypersensitivity in the Pathogenesis of Rheumatic Fever and Periarteritis Nodosa (Lewis Linn McArthur Lecture), *Proc. Inst. Med. Chicago* **15**:270 (March 15) 1945.

10. Gruber, G. B.: Periarteritis Nodosa with Especial Regard to Affection of Gallbladder and Kidneys, *Virchows Arch. f. path. Anat.* **258**:441, 1925.

He had had the first attack of this discomfort about three weeks previous to his hospitalization, but after a day or two it had abated. The physical examination at this time revealed nothing significant except for some tenderness in the area of the left costovertebral angle. Intravenous pyelograms and genitourinary studies revealed no abnormalities. Several days later, the pain began to shift more toward the abdomen, and the patient was transferred to the Peter Bent Brigham Hospital. Here a physical examination proved to be noncontributory with the exception that the sedimentation rate was increased by two to three times normal. No abnormalities were found by roentgenologic examination of the stomach and colon. The patient complained of pain down both legs, but a neurologic examination showed nothing abnormal. After two days, he was discharged from the hospital to his home with a deferred diagnosis, but he returned to the Stillman Infirmary the following day, June 22, 1946, reporting a good deal of pain and discomfort, mainly in the abdomen. His temperature was 101 F. There was some tenderness in the upper region of the epigastrium. Otherwise, with the exception of fever and an elevated sedimentation rate, the physical condition remained normal until July 5, when his blood pressure rose to 150 systolic and 110 diastolic and his white blood cell count to 13,900; there were a few red blood cells in the urine. On July 12 it was felt that the fever and general picture were consistent with a diagnosis of periarteritis nodosa, and because of continued abdominal pain the patient was again transferred to the Peter Bent Brigham Hospital for further study. The gallbladder, a series of gastrointestinal roentgenograms, a motility series and one made after a barium enema all were normal. On July 16 the sedimentation rate was increased to four times normal, although the temperature and blood pressure subsided to within normal limits. There was a transitory elevation of the white blood cell count; for instance, on July 12 it was 14,000, with 9 to 10 per cent eosinophils. The electrocardiogram taken on July 18 showed conspicuous deviation from the previous normal records. It showed an abnormal form of ventricular complex, and the T waves in leads II and III were inverted. These tracings were suggestive of coronary artery disease. By this time it was noted that the patient had suffered a weight loss of 18 pounds (8 Kg.). It was also noted that there were one or two nodules in the vicinity of the brachial artery, not attached to the artery. One of these nodules was excised, and a small piece of the biceps muscle was removed. On examination by the pathologist no abnormality was found.

Within two or three weeks the symptoms abated, the temperature became normal and the patient was discharged from the Peter Bent Brigham Hospital with a tentative diagnosis of periarteritis nodosa.

When last heard from personally, in September 1946, he was in New York and feeling well. Following this communication, he left for London to attend a United Nations Conference but became ill and was admitted to St. Bartholomew's Hospital on November 20. His history at this time was that he had had headache for the previous week and on three occasions convulsive seizures. His blood pressure one week before his admission to the hospital was stated to have been 110 systolic and 70 diastolic. The following is an excerpt from a letter written to us by Dr. G. W. Hayward, of London: "On admission his temperature was subnormal, and there was slight neck rigidity, marked spasm of the abdominal muscles and absent ankle jerks. He was incontinent of urine. His blood pressure was 260 systolic and 160 diastolic. There was no retinitis, and the urine showed a considerable amount of albumin, pus cells and occasional red blood cells. His white blood cell count was 22,000, of which 86 per cent were polymorphonuclear leukocytes. Lumbar puncture showed normal cerebrospinal fluid. His headaches increased, and after three days he complained of marked pain in the left renal angle. His white blood cell count

hemophilia in the family. He had been married for fourteen years and had three children, aged 11, 9 and 4 years. As a child, he had attacks of measles, mumps, whooping cough and chickenpox. Scarlet fever, typhoid, rheumatic fever, bronchitis, pneumonia and pleurisy were not reported.

In 1927, before the patient was seen by my colleagues and me, he entered a sanatorium at Saranac Lake, N. Y., with a diagnosis of bilateral apical tuberculosis. Before this, there was cough, fever, night sweats, rather extensive hemoptysis (1 cupful) and some loss in weight. He was treated without pneumothorax or other collapse therapy and was discharged at the end of a year with his illness arrested; he has had no recurrence up to the present time. Since then the process has been apparently arrested as seen in numerous subsequent roentgenograms.

One pertinent episode which occurred during his stay in Saranac was recalled by the patient. He had a flare-up of fever, and red, tender nodules appeared on the lateral and posterior aspects of both legs, accompanied with pains in the ankle joints. He estimated that the duration of these symptoms was about three weeks.

The patient was first seen by us at the Stillman Infirmary on Sept. 20, 1939. At this time his chief complaints were double vision, headache (paroxysmal in nature and suggestive of migraine), nausea and vomiting. A physical examination revealed no abnormalities. A roentgenogram of the chest showed extensive healed tuberculosis, easily explained by the patient's history. The urine and blood counts were normal. The sedimentation rate of the blood was markedly increased. It is to be noted that whenever the sedimentation rate was determined it was found to be increased to from two to three times normal. Over a period of many years, from 1939 to 1946, whether the patient was experiencing an acute attack or was in a state of recovery this finding was apparent. A roentgenogram of his skull was noncontributory, as were also an electroencephalogram and a lumbar puncture. The headache continued during the patient's stay in the Infirmary. After three days he was discharged with a diagnosis of migraine, which seemed to be relieved by a mixture of sodium salicylate and sodium bromide.

The patient was readmitted to the Stillman Infirmary on the following dates: Oct. 23, 1939 (no diagnosis), Nov. 4, 1939 (diagnosis, migraine) and March 30, 1940 (diagnosis, fatigue, with infection of the upper respiratory tract). In each instance he was hospitalized for from three to seven days and his symptoms were as previously described.

When he was readmitted to the Infirmary on April 22, 1941, he was complaining of fever, sore throat and general malaise. His temperature was 100 F., and there was some nasal congestion and a moderately red throat; a few small cervical glands were noted on both sides. The remainder of the physical examination revealed nothing significant. However, as noted previously, the sedimentation rate showed an increase of about three times normal. On May 9, while still in the Infirmary, the patient complained of some stiffness in his right temporomandibular joint. On examination a large gland was noted, simulating closely the clinical picture of mumps. He remained in the hospital for thirty days with an irregular fever, the temperature being as high as 101 F. during the first twenty days of his illness. It gradually subsided and returned to normal five days before his discharge, at which time no definite diagnosis had been made.

On May 20, 1941, the patient was readmitted to the Infirmary, stating that three days before this date he again noticed fever, general malaise and recurrence of the swelling on the right side of his neck. Physical examination again showed no abnormalities, with the exception of the gland in the neck, and as before the sedimentation rate was increased. On June 4, while he was still in the hospital, some small nodes the size of buckshot were noted under the skin on the right forearm. One of these was removed, and a histologic section proved it to be a lesion of

ciency. It must be remembered that in most of these cases the diagnosis was made at autopsy and that renal impairment was the cause of death. It is apparent that the incidence of this impairment will decline as the diagnosis is made in more instances before death.

DIAGNOSIS

The diagnosis of periarteritis nodosa is difficult of establishment in many instances because in the past the cardinal signs and symptoms of fever, eosinophilia, asthma and renal insufficiency were overemphasized. It is obvious that the symptomatology and the clinical findings are largely related to the arteries involved and to changes in the anatomic structures supplied by these arteries. In the case of F. C., the only consistent symptom was fever. There was no asthma, no evidence of renal insufficiency, no hypertension and no leukocytosis. The diagnosis in this case could easily have been overlooked had it not been for repeated thorough physical examinations and the fact that a great deal of importance was placed on the discovery of a small nodule.

In the case of G. H., although the presence of periarteritis nodosa was strongly suspected before death the diagnosis was not definitely made because the biopsy of a small nodule did not reveal the disease. In retrospect, a biopsy of material from the gastrocnemius muscle may have yielded a definite diagnosis, especially in view of the fact that the patient complained of rather severe pain in both legs. Moreover, the cardinal signs and symptoms of fever, leukocytosis, eosinophilia, renal insufficiency and hypertension did not make their appearance until shortly before death, although a mild degree of leukocytosis and eosinophilia of a transitory nature was apparent while the patient was confined to the Peter Bent Brigham Hospital. The symptomatology in the early part of the illness simulated at times that of a condition within the abdomen requiring surgical treatment, and one might have been led to do an exploratory laparotomy.

In a study of a series of cases of periarteritis nodosa, Spiegel^{16a} stated that "abdominal pain not adequately explained by the involvement of a single organ was the most presenting symptom." In 2 of her cases the diagnosis was made unexpectedly by a demonstration of the lesions in the appendix following appendectomy. Other authors also report that diagnosis was made by finding the lesions of periarteritis nodosa in various abdominal organs following operation.¹⁷ The definite diagnosis of periarteritis nodosa before death has been made in only about 15 per cent of the cases reported. In the other 85 per cent the diagnosis has been made at autopsy. In Spiegel's^{16a} series of 17 cases, the diagnosis was made, as previously stated, in 2 of them by a demonstration of the lesions in the appendix, and in the other 15 the diagnosis

17. Spiegel.^{16a} Gruber.¹⁰

muscular pains similar to the pains he had had before. When he was discharged on the fifty-seventh day in the hospital, he felt subjectively that his muscular aches and pains were definitely decreasing. There was little change revealed by the physical examination, but his condition was improved, although the diagnosis was inactive pulmonary tuberculosis, tuberculosis of cervical lymph nodes and periarteritis nodosa. During his convalescence at the Stillman Infirmary, he remained afebrile and gradually gained strength and weight. On the day of his discharge, on July 27, 1944, he felt well, had no fever or symptoms of any nature and the glands in his neck were hardly palpable. After a week's vacation in New Hampshire, he returned to his laboratory, working eight hours daily.

Since the last-mentioned date, he has been a patient at the Stillman Infirmary four times, and the following diagnoses were made:

Jan. 4 to Jan. 8, 1945:

Diagnosis: infection of the upper respiratory tract, arrested pulmonary tuberculosis, quiescent cervical tuberculous adenitis and inactive periarteritis nodosa

June 1 to June 7, 1945:

Diagnosis: arrested pulmonary tuberculosis, inactive periarteritis nodosa and Meniere's disease (?)

March 25 to March 31, 1946:

Diagnosis: arrested pulmonary tuberculosis, quiescent cervical tuberculous adenitis and inactive periarteritis nodosa

April 20 to May 18, 1946:

Diagnosis: arrested pulmonary tuberculosis, questionably active cervical tuberculous adenitis and inactive periarteritis nodosa

The latest roentgenogram of the chest was taken on March 26, 1946, and showed no change since the last observation. During the four periods of hospitalization mentioned, the patient was only mildly ill; he was slightly febrile at times, but we felt most assured that his periarteritis nodosa was definitely arrested.

It is to be noted that he never had hypertension or an abnormal urine at any time during his years of illness.

On Aug. 15, 1946, when last seen by us for a check-up, he felt well, looked well and had no symptoms. It was at this time that he advised us of the post offered him in China, and it was agreed that there was no reason why he should not accept it.

CASE 2.—G. H., who died suddenly in London of periarteritis nodosa, was a Chinese of 28 years of age. He went abroad in November 1946 feeling well, and, although he had been seen by us previous to this time, the presence of periarteritis nodosa, though strongly suspected, had not been confirmed.

He was born in Canada of Chinese parents, who are alive and well and living in China. He stated that he had one brother living in Canada and one brother who died at the age of 35 years from an unknown cause. He also had three sisters.

The patient's childhood had been uncomplicated by even the usual diseases, and the only history of illness was an appendectomy performed at the age of 23, at which time he also had bronchial pneumonia. In retrospect, it is interesting to note that the appendectomy was performed because of abdominal pain (the patient's chief complaint throughout the present illness), and although we have attempted to obtain further information from the hospital we have been unsuccessful.

In January 1946 he married a Chinese girl of his own age who was born in New York city.

He was a patient at the Stillman Infirmary for the first time in October 1943, at which time the diagnosis was "infection of the upper respiratory tract." His slight temperature elevation quickly subsided, permitting him to leave the hospital in three days.

When next admitted to the Infirmary on June 16, 1946, the patient complained of pain in the left side and flank, similar to the pain suggestive of nephrolithiasis.

PROGNOSIS

The prognosis of such a disease as periarteritis nodosa is most difficult to evaluate. In previous studies, the facts were largely based on postmortem examination. In few cases was the condition diagnosed before death unless there was renal involvement, and then it has been the tendency to predict for the disease an almost 100 per cent fatality rate. As there is more awareness of this illness, especially when the diagnosis is made in cases in which there is no asthma or renal involvement, the prognosis must be altered.

In the case of F. C., no evidence of renal involvement was present at any time, and from clinical study the only arteries involved were those supplying the peripheral muscles of the extremities and possibly the cerebral arteries. At the time when the condition was originally diagnosed it was felt that the outlook was hopeless and that his illness would soon prove fatal. However, after several months of rest in bed, which, in retrospect, probably arrested the activity of the cervical tuberculous adenitis and caused a cessation of the progress of the periarteritis nodosa, he was able to resume normal activities except at the times when the tuberculous adenitis was reactivated. It is my opinion that this patient will remain comparatively well as long as he restricts his activities to the level at which his cervical tuberculous adenitis remains quiescent. He is now alive and well six years after the original diagnosis was established. After a careful study of the literature, this is found to be the only definitely proved instance (along with those reported by Motley¹⁹ and Fitz²⁰) of a recovery which left the patient not only alive and well but able to practice his profession. Motley,²¹ in a report of 2 cases in which the diagnosis was also made by biopsy of peripheral nodes, stated that 1 patient died suddenly of a coronary occlusion and the other¹⁹ allegedly recovered entirely and was clinically well in 1944. Fitz and others²⁰ reported a case in which the disease was of unusually long duration, lasting from 1929 to 1935, a period of six years. The diagnosis was made by reexamination of the gallbladder and appendix, both of which had been removed previously. Fitz recalls the patient whom Parkhurst²² reported on and who lived for six years after the diagnosis was made by nodular biopsy.

Although there are many cases in the literature in which longevity has been reported and in which the patients were apparently well for three or four years after the establishment of the diagnosis, personal

19. Motley, L.: Periarteritis Nodosa with a Report of a Case Showing Unusual Features and Apparent Recovery, *J. A. M. A.* **106**:898 (March 14) 1936.

20. Fitz, R.; Parks, H., and Branch, C. F.: Periarteritis Nodosa: Report of a Case, *Arch. Int. Med.* **64**:1133 (Dec.) 1939.

21. Motley, L.: Personal communication to the author.

22. Parkhurst, A. R.: Personal communication to the author.

remained elevated, and edema of the left loin appeared twenty-four hours later. He was afebrile at this time.

"In view of the renal tenderness, renal edema, leukocytosis and urinary changes, it was thought that he had a left perinephric abscess, and the left kidney was explored. At operation there was a large perirenal hematoma containing about 3 pints (1,419 cc.) of blood, and the left kidney was studded with small white infarcts. Following operation his blood pressure was raised to 280 systolic and 170 diastolic, and bilateral papilledema with retinal hemorrhages developed. The blood urea was 66 mg. per hundred cubic centimeters, and the urinary findings were as before. There was a recurrence of bleeding, and a left nephrectomy was carried out, but the patient died two days after operation.

"Autopsy confirmed the diagnosis of periarteritis nodosa. The kidneys showed multiple small infarcts, and there were small aneurysms in the mesenteric vessels, both coronary vessels and middle cerebral artery. There was still a small left renal hematoma.

"The interesting features of this patient were the sudden development of a severe degree of hypertension, the marked leukocytosis without eosinophilia and the cerebral symptoms which caused his admission to the hospital."

SYMPTOMATOLOGY

The symptomatology of periarteritis nodosa is such that it is unwise to list symptoms and signs as being characteristic of this illness. The overemphasis on the cardinal symptoms of the illness has in the past been responsible for the lack of diagnosis in many cases. This is primarily an arterial disease, and the symptoms depend on the organs involved. In the case of F. C., the migraine of which he complained in all probability was due to involvement of some of the cerebral arteries. He evidently had no involvement of the pulmonary or renal arteries and therefore had no asthma or evidence of renal insufficiency. Frequent blood pressure readings were always in the normal range, and at no time during his frequent hospitalizations did he have leukocytosis. Moreover, he never complained of abdominal pain or discomfort, which would lead to the belief that there was no involvement of arteries supplying the abdominal organs. F. C.'s main symptoms were weakness and fever with, at times, indefinite pains in the extremities. It would seem from his whole clinical picture that the arteries involved were probably those of the brain and the superficial arteries supplying the muscles of the extremities.

In contrast, G. H.'s symptoms were those of involvement of arteries supplying the abdominal organs (as manifested by abdominal pain), arteries supplying the muscles of the legs (causing muscular pain) and finally arteries involving the kidneys resulting in considerable renal impairment, hypertension and death.

The incidence of renal impairment in the literature is listed as high as 80 per cent.¹⁶ Eighty-three of Gruber's 115 patients had renal insuffi-

16. (a) Spiegel, R.: Clinical Aspects of Periarteritis Nodosa, *Arch. Int. Med.* 58:993 (Dec.) 1936. (b) Footnote 2.

AMBULATORY MANAGEMENT OF AZOTEMIA AND CLINICAL UREMIA

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DURING a nine month period, 21 patients with azotemia and clinical uremia having serum creatinine concentrations of over 3 mg. and serum urea concentrations of over 80 mg. per hundred cubic centimeters were treated in the Clinic for Renal Disease of the Stanford University School of Medicine. Their illnesses varied in severity from azotemia without symptoms to frank clinical uremia. Most of these patients were in the terminal stage of glomerular nephritis. One patient had polycystic kidneys, and 1 had chronic uremia of obscure origin.

It has been our experience, which is in conformity with past experience gained in the Clinic, that such patients can be managed satisfactorily on an ambulatory basis until the final stages of renal failure. In addition, the irregular and unpredictable course of severe chronic renal insufficiency has impressed on us the fact that there is always some hope that the patient may continue to lead a useful life for some time.

DIETARY MANAGEMENT

The patients were maintained on a diet containing 0.5 Gm. of protein per kilogram of body weight per day. To this was added an amount equal to the protein lost in the urine. On each visit to the Clinic the figure for the latter was obtained from quantitative determinations of the urine protein by the precipitate method of Addis.¹

The patients were taught how to estimate the protein content of their diets quantitatively and were given a simplified booklet of protein values for common foods based on household measures. They were advised to take no meat, fish or fowl and to avoid soups and gravies prepared from these items. This regimen permitted them to use their few grams of protein with more latitude for other foods. In addition,

From the Department of Medicine, Stanford University School of Medicine.

1. Addis, T.: Glomerular Nephritis, New York, The Macmillan Company, to be published.

was made at autopsy. Bernstein's¹⁸ report bears out the experience of the authors already referred to in the relationship between the antemortem and postmortem diagnoses.

The value of the sedimentation rate in the diagnosis of periarteritis nodosa has not been definitely established. However, in both of the patients under discussion in this report the sedimentation rate was constantly increased despite the fact that all other clinical and laboratory examinations gave normal results.

The diagnosis is difficult of establishment due to the complexity of the clinical picture, but it is apparent that as physicians become more aware of this illness and as a more thorough investigation is made in patients suspected of having this condition the instances of antemortem diagnosis will increase. However, periarteritis nodosa is to be considered as a possibility in any continued illness, and while the symptoms may be related to any of the organs involved, no symptoms of any one disease may be present. In some cases the diagnosis can be confirmed by biopsy of a subcutaneous nodule, by biopsy of material from the gastrocnemius muscle or by laparotomy.

ETIOLOGY

The etiology of periarteritis nodosa is not definitely established, although the work of Rich, Cohen, Rackemann and others seems to point to the fact that the most likely cause of this condition is an allergic manifestation. In the case of F. C., it is my opinion that the disease was an allergic response to active glandular tuberculosis. The course of his illness and the definite, apparently coincidental, relationship of the appearance of periarteritis nodosa following the activation of his tuberculosis on several occasions would seem to make this a likely possibility. So far as is known, this is the only reported case in which the condition seems to be related to a tuberculous infection. Dr. S. Howard Armstrong said, in his discharge appraisal of this patient from the Peter Bent Brigham Hospital: "Although I have seen no reports of periarteritis in association with active tuberculosis, there is no reason why such an infection, in releasing foreign proteins, might not be as capable of producing this reaction as the various foreign proteins employed by Rich."

In the case of G. H., no basic condition was found with which the lesions of periarteritis nodosa could be associated.

Until more work has been done on the etiology of periarteritis nodosa, it must be assumed that the inciting factor is on the basis of an allergy and everything possible must be done in an effort to find the causative antigen.

18. Bernstein, A.: Periarteritis Nodosa Without Peripheral Nodules Diagnoses Ante Mortem, *Am. J. M. Sc.* **190**:317 (Sept.) 1935.

At the end of the first week the serum creatinine level was unchanged, but the serum urea was 44.2 mg. per hundred cubic centimeters, and the twenty-four hour excretion of protein had dropped to 13.2 Gm. One month later the creatinine concentration had decreased markedly and the urinary protein excretion was only 7.7 Gm. in twenty-four hours. In addition, the urinary sediment showed a considerable diminution in the number of renal failure casts.

AMBULATORY CARE VERSUS HOSPITAL CARE

We have found that the long and unpredictable course makes it impractical to hospitalize the patients, except terminally and as a last

*Effect of an Adequate Low Protein Diet on Patients Whose Diet Had Not Been Restricted Previously.**

Patient	Date	Weight, Kg.	Daily Diet Protein, Gm.	Serum Urea, Mg. per 100 Cc.	Serum Creatinine, Mg. per 100 Cc.	Blood Pressure	Clinical Symptoms
O. O.	10/ 8/40	84.3	80	43	190/110	
	11/14/40	50	22	150/100	Subjectively improved
E. H.	1/25/45	83.2	Over 80	64	2.40	115/ 95	Edema, nausea and weakness
	2/15/45	45	46	115/ 95	Nausea and weakness diminished
T. L.	12/ 4/45	70.4	Over 80	83	155/105	
	12/11/45	45	59	145/ 80	No change
R. Y.	4/ 2/46	76.2	Over 80	92	180/125	Considerable dyspnea and weakness
	4/13/46	55	67	180/110	Dyspnea and weakness much improved †
M. B.	4/ 9/46	66.4	Over 80	98	3.59	150/100	Felt well ‡
	4/20/46	40	46	2.90	140/ 96	
J. M.	9/28/46	63.1	Over 60	..	14.40	192/120	Nausea, weakness and exertional angina
	10/ 5/46	35	172	10.97	204/120	Nausea improved, other symptoms unchanged
H. C.	11/16/46	69.8	Over 80	136	4.71	210/160	Dyspnea on slight exertion
	12/ 7/46	40	38	4.71	148/ 82	Much improved †
C. P.	12/19/46	76.6	Over 80	163	5.24	200/135	Weakness and nausea
	1/ 2/47	55	58	4.71	170/130	Improved
V. M.	5/13/47	72.2	70	74	6.68	170/120	Weakness, nausea and twitching
	5/27/47	20 §	..	7.34	160/110	Dramatically improved
J. D.	5/29/47	68.2	80	101	6.75	184/130	Nausea, headache and weakness
	6/ 5/47	20 §	75	7.05	168/118	Subjectively improved

* The protein content of the diet before treatment was estimated from a diet survey.

† Digitalis was administered for cardiac failure.

‡ This patient had chronic uremia for which no cause had been found.

§ A very low protein diet was used for one week only, and the amount was then raised to 40 Gm. daily.

resort. They can be handled well as outpatients. They may be capable of leading relatively normal lives in spite of the presence of azotemia, anemia and associated symptoms of clinical uremia. One of our patients has been attending law school during a period when his serum creatinine has varied from 6 to 10 mg. per hundred cubic centimeters (case 3). Such persons are much happier when assisted to lead lives which, though activity is limited, are as normal as possible.

attempts by correspondence to obtain further information have not met with success.

Weiss²³ stated that "it is probable that the prognosis will improve when the disease is oftener recognized clinically."

From a review of the literature and from personal experience, it seems apparent that when the disease involves the arteries of the lungs, kidneys or abdominal viscera the prognosis is grave. In the case of G. H., the arteries of the abdominal viscera and the coronary arteries were undoubtedly affected early in the illness, although no definite involvement of the renal arteries was apparent at this time. He had a temporary remission. However, his death within six months after the onset of symptoms was inevitable, and the observations at autopsy proved the widespread involvement of the arteries of the abdominal viscera, the heart and the kidneys.

In contrast, it is probable that many cases of periarteritis nodosa manifest themselves solely by involvement of peripheral arteries not supplying vital organs. The disease arrests itself spontaneously, or with the removal of a possible antigen the patient recovers. Thus, if the diagnosis is based solely on the biopsy of a peripheral nodule or muscle, without clinical manifestations of renal, pulmonary or abdominal involvement, the prognosis should be considered more favorable.

SUMMARY AND CONCLUSION

Two highly contrasting cases of periarteritis nodosa are described, both involving members of the Chinese race. Although the medical literature on the subject of this disease was thoroughly and carefully studied, there was no other mention found of a member of the Chinese race with periarteritis nodosa. But it is nevertheless interesting to note that in the twelve year period from 1935 to 1947 we have had under medical observation at Harvard University approximately 80,000 students and these two Chinese men were the only ones who had periarteritis nodosa in the entire student body. The number of Chinese students at Harvard University is small, making up only about 1 per cent of the total.

In 1 of the patients, F. C., the etiologic factor is assumed to have been a tuberculous antigen. This patient is apparently well and active six years after the establishment of the diagnosis by biopsy of a peripheral nodule. In the second patient, G. H., no evidence of allergy could be found, and although the diagnosis was strongly suggested it was not proved until the autopsy.

The symptomatology, diagnosis, etiologic factors and prognosis of periarteritis nodosa have been discussed.

23. Weiss, S.: Arteritis: Disease Associated with Inflammatory Lesions of the Peripheral Arteries, *New England J. Med.* **225**:579, 1941.

ACIDOSIS

Patients in advanced renal failure tend to exhibit acidosis, which may become severe. Development of acidosis is due principally to two factors. The tubules fail in their ability to excrete sulfate and phosphate ions, so that these accumulate in the body. The tubules also fail in their ability to reabsorb sodium and to produce ammonia, which normally spares the fixed bases. Nausea and anorexia, with diminished fluid consumption, further aggravate the situation. Other factors may operate to a lesser degree.

In the practical management of uremia, acidosis should not be a problem until the last stages. If a large fluid consumption is maintained, with a copious flow of urine, and if enough salt is allowed in the diet to replace that lost in the urine, the homeostatic mechanisms of the body will maintain an adequate acid-base balance. In the last stages of uremia, when the patient loses his ability to drink and eat, acidosis may become difficult to control except through the parenteral administration of fluids.

SEDATION

Sedation is of use in the control of nausea, muscular hyperexcitability and convulsions. Paraldehyde has the disadvantages associated with its odor and with pulmonary excretion, but it is an ideal sedative in uremia. Its metabolism does not involve the kidney, and it is excreted rapidly. If barbiturates are used, it is essential to select those, such as sodium pentobarbital and "seconal sodium" (N.N.R.) which are short acting and are destroyed principally by the liver. It is necessary to watch closely for cumulative effects. When muscular twitchings and convulsions are the result of low serum calcium concentration, the intravenous administration of calcium salts may relieve symptoms for a short time.

DIARRHEA

Persons with pronounced retention of urea may suffer from severe watery diarrhea, which may contain blood. This may result from excretion of urea into the bowel. There urea-splitting organisms liberate ammonia, which is capable of greatly irritating the mucosa. Confirmation of this idea may be found in the fact that a change in the flora and in the reaction of the bowel through the use of *Lactobacillus acidophilus* preparations usually causes considerable improvement in the diarrhea. Patients should be cautioned that in the event of the development of diarrhea or nausea and vomiting medical aid to replenish the salt, restore fluid balance and combat acidosis should be sought immediately.

CARDIAC FAILURE

Patients presenting themselves with azotemia and clinical uremia may at the same time have the situation complicated by the presence of

there is some reason to believe that purines and nucleoproteins of animal origin are harmful to the kidneys.²

So as to insure an adequate consumption of vitamins and minerals, a daily increment of these necessary factors was prescribed in the form of a polyvitamin and polymineral preparation.

Whereas the strict limitation of salt consumption may be desirable in hypertension without uremia and may be essential in the degenerative stage of glomerular nephritis with edema, it may be dangerous in the presence of severe renal failure. Diminished tubular function depresses the reabsorption of sodium, and severe symptoms of sodium depletion may result if dietary restriction is excessive. The salt consumption, therefore, should not be reduced below 5 Gm. daily.

It is desirable to maintain high calory consumption, and this is done by the liberal use of fats and carbohydrates. Candy, cream, corn starch puddings and fruit juices fortified with lemon juice and sugar all provide sources of energy with little protein.

Fluid consumption should be maintained at a high enough level so that a large volume of dilute urine is produced, preferably about 3,000 cc. daily. Patients are encouraged to drink water and carbonated beverages at frequent intervals.

The value of reducing the dietary protein cannot be overestimated. Patients are frequently seen in the Clinic who have been on a high protein diet and are in severe clinical uremia, with drowsiness, muscular hyperexcitability, collapse and high serum urea and creatinine concentrations. Within a few days after institution of an adequate low protein diet the clinical condition improves, the serum urea concentration drops precipitously and the creatinine concentration may decline to a lesser degree. This effect in 10 patients is demonstrated in the accompanying table. The remaining patients in the series were not suitable for this demonstration since azotemia or clinical uremia developed while they were on adequate low protein diets as a result of progress in the renal lesion.

CASE 1.—C. P. is a 41 year old male drug clerk with known albuminuria and edema of the ankles since 1929. He was first seen in the Clinic on Dec. 19, 1946, for severe headache, dyspnea and hypertension of nine months' duration. He had been advised to take a high protein diet with much meat.

On the first visit the serum creatinine was 5.24 mg. and the serum urea was 163 mg. per hundred cubic centimeters. He had the urinary sediment of renal failure, with broad casts, and a remarkably high protein excretion of 26.2 Gm. in twenty-four hours. His weight was 76 Kg.

He was placed on a diet containing 20 Gm. of protein daily with no meat for one week and thereafter 55 Gm. of protein daily with 5 Gm. of salt and no limitation of calories. He was also given supplementary vitamins and minerals.

2. Newburgh, L. H., and Johnston, M. W.: High Nitrogen Diets and Renal Injury, *J. Clin. Investigation* 10:153-160 (April) 1931.

the hematocrit reading was 23 mm. and the urinary sediment showed many broad casts of the type seen in renal failure. He felt weak and fatigued easily, and he entered the hospital for transfusions of whole blood and red cells.

Following the transfusions, he did not feel much better, although the hematocrit reading rose to 35 mm. His serum creatinine level rose to 9.88 mg., and the serum urea level was 143 mg. per hundred cubic centimeters. Watery diarrhea developed which was troublesome. The hematocrit reading rapidly dropped back to 23 mm. in one month.

On March 18 he was given transfusions of concentrated red cells and whole blood. The hematocrit reading responded promptly, but his subjective response was again poor. The diarrhea, however, was completely relieved by daily administration of a *Lactobacillus* preparation (yoghurt).

Because of the failure in subjective response to blood, the patient refused further transfusion. The hematocrit reading fell to 23 mm. again on May 6. He said that once it was stabilized at the low level he felt better and had more energy.

At this point there was a remarkable change in his course, and, with no change in treatment, he began to improve. Although the hematocrit reading was still only 24 mm. on June 3, his serum creatinine had fallen to 3.82 mg. per hundred cubic centimeters. The character of the renal sediment had altered completely, with appearance of oval fat bodies. The excretion of protein fell from levels of 10 to 15 Gm. to 2.6 Gm. in twenty-four hours. Excretion of erythrocytes fell from 1,545,000,000 to 18,000,000 in twenty-four hours, and the endogenous creatinine clearance rose from 12.7 to 23.7 per cent of normal. He feels much better and is pursuing his studies with renewed vigor.

COMMENT

There has been much debate in the past concerning the minimum amount of protein in the diet required to maintain health. At the time of Lusk's classic work the accepted figure was from 1.0 to 1.5 Gm. of protein per kilogram of body weight per day. Subsequently, Sherman³ determined the requirement to be 0.5 Gm. per kilogram per day. Hegsted and others⁴ confirmed that figure. In order to maintain the level safely above the minimum requirements, we have used 0.5 Gm. per kilogram per day, to which is added an amount equal to that lost in the urine.

Addis,⁵ Newburgh⁶ and Borsook and Winegarden⁷ have stressed the fact that excretion of urea plays a preponderant role in determining

3. Sherman, H. C.; Gillett, L. H., and Osterberg, E.: Protein Requirement of Maintenance in Man and the Nutritive Efficiency of Bread Protein, *J. Biol. Chem.* **41**:97-109 (Jan.) 1920.

4. Hegsted, D. M.; Tsongas, A. G.; Abbott, D. B., and Stare, F. J.: Protein Requirements of Adults, *J. Lab. & Clin. Med.* **31**:261-284 (March) 1946.

5. Addis, T.: The Osmotic Work of the Kidney and the Treatment of Glomerular Nephritis, *Tr. A. Am. Physicians* **4**:223-229, 1940; The Treatment of Chronic Renal Insufficiency, *J. Urol.* **41**:126-136 (Feb.) 1939.

6. Newburgh, J. D.: The Changes Which Alter Renal Osmotic Work, *J. Clin. Investigation* **22**:439-446 (May) 1943.

7. Borsook, H., and Winegarden, H. M.: The Work of the Kidney in the Production of Urine, *Proc. Nat. Acad. Sc.* **17**:3, 1931.

In general, the degree of activity permissible depends on the patient's own judgment. Weakness and dyspnea are the signals that advise him to reduce his activity.

At the end of the illness, hospitalization may of course become necessary to relieve nausea, muscular twitching, convulsions and other terminal events.

CONTROL OF ANEMIA

The progressive anemia which accompanies azotemia and which can almost be considered an index of the course at times becomes troublesome. There may be a critical level for the patient, below which he is uncomfortable. Because of diminished oxygen-carrying capacity of the blood when the hematocrit reading falls below this critical level, the patient may experience weakness, dyspnea and at times anginal pain. Such symptoms may be relieved rapidly by transfusion of whole blood or preferably of concentrated red cells. Since the latter preparation contains little protein in solution, it does not overload the circulation with a sudden increase in blood volume.

CASE 2.—F. G. was a 47 year old housewife who was found to have polycystic kidneys in 1932. She was followed in the Clinic from 1935 until her death in February 1947.

She was placed on a diet containing 40 Gm. of protein per day without meat. Her weight was about 52 Kg., and the urinary protein excretion was less than 1 Gm. in twenty-four hours. When she was first seen the serum urea concentration was 31.4 mg. per hundred cubic centimeters, the hematocrit reading was 38 mm. (Wintrobe) and her blood pressure was 210 systolic and 90 diastolic.

There was little change in her condition until 1941, after the uneventful birth of a child. From that time on the serum urea concentration slowly rose and the value for the hematocrit reading gradually declined. Her blood pressure remained unchanged. In October 1945 the hematocrit reading had fallen to 23 mm., the serum creatinine concentration was 10.97 mg. per hundred cubic centimeters and she complained of dyspnea, weakness and anginal pain on exertion. A loud diastolic murmur was heard along the left sternal border. She was given 4 pints (1,892 cc.) of whole blood, which relieved all her symptoms and returned the hematocrit reading to 38 mm.

She did not require transfusion again until November 1946 and again in January 1947. Each time the indications were a decrease in the hematocrit reading to 23 mm., with a return of dyspnea and exertional angina. Transfusions brought rapid relief.

There are persons, however, for whom the use of transfusions not only is of little avail but also may actually increase discomfort. In one case (case 3) transfusion was followed by a rapid return of the hematocrit reading to low levels. During the period of fall, the patient complained of increased weakness and dyspnea, which disappeared after the low level was stabilized.

VASCULAR RESPONSES IN MAN TO LIGATION OF THE INFERIOR VENA CAVA

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AND

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NEW ORLEANS

LIGATION of the inferior vena cava for phlebothrombosis and thrombophlebitis is not a new therapeutic procedure. The first ligation was performed by Kocher in 1883 and the second two years later by Billroth.¹ There have been few papers² on the subject until recently. Since publication of the article by Collins and others,³ however, there have been a considerable number of reports.⁴

This procedure would seem drastic to most clinicians. Nevertheless, it has been used without apparent serious disturbances clinically. Since ligation of the inferior vena cava is being performed in greater numbers, it is imperative that certain physiologic observations be made to evaluate the circulatory adjustments. There have been fairly extensive observations on experimental animals⁵ but relatively few in man. In fact,

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1. Plaff, O. G.: Ligation of the Inferior Vena Cava, *Am. J. Obst. & Gynec.* **11**:660-663, 1926.

2. Krotoski, J.: Zur Venenunterbindung bzw.-extirpation bei der puerperalen allgemeininfektion vom chirurgischen Standpunkt, *Chirurg* **9**:425-439, 1937; cited by Moses.^{4c} Ochsner, A., and DeBailey, M.: Therapeutic Considerations of Thrombophlebitis and Phlebothrombosis, *New England J. Med.* **225**:207-227, 1941.

3. Collins, C. G.; Jones, J. R., and Nelson, E. W.: Surgical Treatment of Pelvic Thrombophlebitis: Ligation of Inferior Vena Cava and Ovarian Veins; Preliminary Report, *New Orleans M. & S. J.* **95**:324-329, 1943.

4. (a) Gaston, E. A., and Folsom, H.: Ligation of the Inferior Vena Cava for the Prevention of Pulmonary Embolism, *New England J. Med.* **233**:229-233, 1945. (b) O'Neil, E. E.: Ligation of the Inferior Vena Cava in the Prevention and Treatment of Pulmonary Embolism, *ibid.* **232**:641-646, 1945. (c) Moses, W. R.: Ligation of the Inferior Vena Cava or Iliac Veins, *ibid.* **235**:1-7, 1946.

5. Polkey, H. J.: The Phenolsulphonephthalein Output After Ligation of the Vena Cava and Renal Veins, *Urol. & Cutan. Rev.* **33**:294-297, 1929. Whittenberger, J. L., and Huggins, C.: Ligation of Inferior Vena Cava, *Arch. Surg.* **41**:1334-1343 (Dec.) 1940.

cardiac failure. In contrast to the cardiac failure which is associated often with the initial stage of glomerular nephritis and is probably the result of a sudden increase in blood volume, the cardiac failure associated with uremia is usually the result of chronic hypertension, with left ventricular hypertrophy and insufficiency.

Cardiac failure in the presence of uremia should be treated by digitalization and by any other ordinarily indicated measures except the further limitation of salt consumption. With improvement in cardiac status, a parallel improvement in azotemia and renal clearances may result. This may be due to improved circulation to the kidney, with the relief of congestion in the renal veins.

PROGNOSIS

A definite prognosis cannot be offered to a patient with azotemia or uremia. In no medical condition may the end seem more inevitable. Yet the course may confound and amaze the physician. It is true that of the 21 patients observed during the past nine months 2 have died and the fate of 2 others, who when last seen were approaching the moribund condition, is uncertain. On the other hand, in 2 patients who have been followed for some time with elevated serum urea and creatinine levels progressing upward from visit to visit and with clinical symptoms of advanced uremia the process has suddenly reversed and the improvement is striking. The following case is illustrative.

CASE 3.—R. Y. is a 28 year old law student and retired naval officer. In October 1944 a routine physical examination revealed albumin, granular casts, leukocytes and red blood cells in his urine. He was studied in naval hospitals and told that he had chronic nephritis, for which he was retired. There was no knowledge of any initial episode, and previous examinations had failed to reveal abnormalities.

He was kept on a high protein diet until he came to the Clinic on April 2, 1946. He was found then to be in the terminal stage of glomerular nephritis. His blood pressure was 180 systolic and 125 diastolic, the serum urea 92.3 mg. per hundred cubic centimeters, the total serum protein 5.77 Gm. per hundred cubic centimeters and the hematocrit reading 28 mm. (Wintrobe). The specific gravity of the urine was 1.010, and he was excreting 10.5 Gm. of protein, 60,000,000 leukocytes and 630,000,000 erythrocytes in twenty-four hours. Few casts were seen. He weighed 76 Kg. There was moderate pitting edema, and the liver extended two fingerbreadths below the costal margin. His heart was enlarged, with regular rhythm and no murmurs.

He was digitalized and placed on a diet containing 55 Gm. of protein per day without meat, with no limit on calories and with salt restricted to 5 Gm. daily. He improved rapidly, with loss of edema and a drop of the serum urea to 48 mg. per hundred cubic centimeters. On May 4, 1946, the serum creatinine concentration was 2.96 mg. per hundred cubic centimeters.

He felt well enough to play golf and enroll as a law student with a full schedule, although he was counseled against overtaking himself. The serum creatinine level rose steadily during the succeeding months, reaching 7.90 mg. on Jan. 4, 1947. At that time the serum urea was 125 mg. per hundred cubic centimeters,

Results.—The results are summarized in table 1. In only 1 instance was there no elevation in venous pressure following the operation (case 10). Initially, the venous pressures varied from 120 to over 600 mm. of water, or from 60 mm. below to over 425 mm. above the mean normal values.⁹ There was a gradual decline in venous pressure

TABLE 1.—*Venous Pressure (Millimeters of Water) in Veins of the Extremities and Abdominal Wall of Twelve Patients with Ligation of the Inferior Vena Cava*

Case	Age, Yr.	Race	Date of Measure- ment	Ante- cubital	Vein				Date of Operation
					Dorsal Pedal		Right Abdom- inal	Left Abdom- inal	
					Right Foot	Left Foot			
1	21	W	4/11/42	122	...	248	3/19/42
2	31	N	5/20/42	...	360	500+	5/ 2/42
			6/24/42	106	356	366	
3	21	W	5/22/42	110	416	506	4/30/42
			3/ 9/43	140	200	220	
			3/ 6/46	120	320	330	
			10/18/46	120	300	280	...	202	
4	67	W	4/20/42	26	...	244	3/28/42
			6/30/42	106	...	306	
			11/ 7/42	50	300	300	
			2/12/46	120	210	210	
5	27	W	4/28/42	112	...	320	4/25/42
			5/ 7/42	140	...	290	
			6/ 1/42	126	...	256	
			11/10/42	100	170	180	
			3/20/46	120	200	190	
			10/15/46	140	180	185	
6	34	W	2/27/46	130	330	330	6/14/42
			10/21/46	128	322	314	60	80	
7	45	N	2/20/46	120	420	340	2/ 5/46
			4/29/46	110	314	280	
			6/13/46	120	280	280	
			8/12/46	90	420	340	
			10/15/46	110	420	360	170	170	
8	22	N	2/ 6/46	100	462	600+	12/21/45
			5/ 2/46	100	480	600+	
			10/15/46	120	430	320	140	120	
9	26	W	5/25/46	120	300	320	5/25/46
			10/18/46	120	306	240	...	254	
10	27	N	4/ 3/46	110	120	120	3/20/46
			5/11/46	80	120	120	
11	43	N	10/18/46	110	316	320	...	220	6/26/46
12	36	N	6/13/46	100	220	200	6/13/46
			6/15/46	100	300	250	
Mean.....				110	306	302	123	174	
Maximum.....				140	480	600+	170	254	
Minimum.....				26	120	120	60	80	

toward normal, but it returned to within the maximum limits of normal in only 2 instances (cases 4 and 5). The average decline in four years was 69 mm. of water in the right foot and 135 mm. in the left. The

9. Winsor, T., and Burch, G. E.: Use of the Phlebomanometer: Normal Venous Pressure Values and a Study of Certain Clinical Aspects of Venous Hypertension in Man, *Am. Heart J.* **31**:387-406, 1946.

the osmotic work done by the kidneys in the secretion of urine. In view of the fact that protein in excess of anabolic needs is deaminized to form urea, it seems reasonable to suppose that protein in excess of that needed for the body economy will sharply increase the work of the kidneys.

Experimentally, this has been confirmed by Addis and others,⁸ who studied the effect of dietary protein on rats from which three quarters of the kidney substance had been removed by operation. They found that a diet adequate but not excessive in protein maintained the rats in good health without nitrogen retention. However, increasing the dietary protein content by increments created and increased nitrogen retention, until, at the highest dietary levels, the rats died with steadily mounting azotemia and uremia.

Since osmotic work is a function of concentration gradients, the desirability of a large urine volume with relatively low concentrations of solutes seems self evident.

We believe that the management of uremia is best served by the positive measures proposed. With their use, life may be prolonged and the patient may be made comfortable to the maximum possible degree.

SUMMARY

Twenty-one patients with azotemia and clinical uremia have been studied during nine months.

A program of positive measures for management is offered, based on an adequate low protein diet and a high urine volume.

8. Addis, T.; Barrett, E.; Lew, W.; Poo, L. J., and Yuen, D. W.: Danger of Intravenous Injection of Protein Solutions After Sudden Loss of Renal Tissue, *Arch. Int. Med.* **77**:254-259 (March) 1946.

they maintained an erect posture throughout the day. The degree of the edema and the height of the venous pressure were not proportional in these patients. Such findings indicate the efficient compensatory mechanisms concerned locally with water balance in tissues.

An interesting factor was the absence of abnormal dilatation of the veins of the legs and the feet even in the presence of pronounced venous hypertension. In fact, in some instances the veins were smaller than normal, indicating severe venous spasm. Biopsy of veins from the foot of a patient (case 9) showed a "functional phlebomesohyperplasia" (details to be described elsewhere). This is probably the result of continuous venous "spasm" over many months.

The definite venous hypertension in the superficial low abdominal veins in 5 of 6 patients studied indicates the development of venous collateral flow through these veins. In every instance the direction of blood flow was cephalad instead of caudad.

PLETHYSMOGRAMS

A quantitative study of the variations in volume of the tips of the fingers and toes was performed plethysmographically.¹⁰ All values recorded by the plethysmograph are expressed in cubic millimeters of volume change per 5 cc. of part. The volume changes in response to general environmental cold (room temperature 63 F. and relative humidity 55 per cent) and heat (temperature 110 F. and humidity 55 per cent) were recorded in addition to the volume changes in a comfortable room atmosphere (temperature 78 F. and relative humidity 55 per cent). The right index finger was observed as a control. The effect of the psyche on vascular responses was reduced to a minimum by the avoidance of noises, the removal of the plethysmograph and other equipment to an adjoining room and the use of a specially constructed room for the subject.¹¹

Section of the lumbar sympathetic nerves¹² was not performed in cases 1 to 6 inclusive. The operation was confined to the right side in cases 7 and 10.

10. Burch, G. E.: A New Sensitive Portable Plethysmograph, *Am. Heart J.* **33**:48-75, 1947.

11. Neumann, C.; Cohn, A. E., and Burch, G. E.: A Study of the Influence of the Character of an Examining Room on the Peripheral Blood Vessels of Normal, Hypertensive, and Senile Subjects, *J. Clin. Investigation* **21**:651-654, 1942.

12. Section of the lumbar sympathetic nerves performed at the time the vena cava was ligated consisted of sectioning the lumbar sympathetic chain at the level of the fourth lumbar vertebra.

there has been only one preliminary report⁶ devoted to the study of vascular responses to ligation of the inferior vena cava. It is the purpose of this presentation to describe certain types of studies directed to clarify the circulatory readjustments in man precipitated by sudden occlusion of the inferior vena cava.

METHODS •

These observations are limited to 12 patients, all women (table 1 indicates the variations in age and race), in whom the inferior vena cava had been ligated by Dr. C. G. Collins, of the Department of Gynecology and Obstetrics of the Tulane University of Louisiana School of Medicine, in the treatment of pelvic thrombophlebitis. The severity of the illness prevented the removal of the patients to our laboratory early after operation. As soon as the patients' postoperative condition permitted, they were moved to the laboratory with controlled atmospheric conditions. The observation room is quiet and draft free.

The patients were transported to the laboratory on a roller when they were not ambulatory. They rested for at least thirty minutes in a hospital-type bed before any observations were made. They removed all except their underclothing and were covered with a sheet to an extent necessary for comfort. The underclothing was loosened to prevent constriction and interference with the circulation. The duration of each period of observation did not exceed two hours, thus avoiding fatigue. There were no medications administered during the day of study, and observations were not begun until at least two hours after the patients had eaten.

The methods and details for each type of observation are discussed separately. Some of the patients have been observed for as long as four and one-half years.

VENOUS PRESSURE

The phlebomanometer⁷ was used to determine the venous pressure. All determinations were carried out with the vein at the phlebostatic level.⁸ The determinations were made in the dorsal venous arch of each foot, the superficial abdominal veins bilaterally and the antecubital vein unilaterally.

6. Burch, G. E., and Winsor, T.: Physiological Studies on Five Patients Following Ligation of the Inferior Vena Cava, *Proc. Soc. Exper. Biol. & Med.* **53**:135-138. 1943.

7. Burch, G. E., and Winsor, T.: The Phlebomanometer: New Apparatus for Direct Measurement of Venous Pressure in Large and Small Veins, *J. A. M. A.* **123**:91-92 (Sept. 11) 1943.

8. Winsor, T., and Burch, G. E.: Phlebostatic Axis and Phlebostatic Level: Reference Levels for Venous Pressure Measurements in Man, *Proc. Soc. Exper. Biol. & Med.* **58**:165-169. 1945.

were still below the normal mean.¹³ The mean volumes of the pulse deflections in the patients who underwent section of the sympathetic nerves were 3.5 cu. mm. for the right toe and 3.9 cu. mm. for the left, with maximums of 8.3 and 6.6 respectively. These values compare favorably with the normal. Ligation of the inferior vena cava modified by section of the lumbar sympathetic nerves resulted in a greater magnitude of the pulse deflections. The tip of the left toe of the patients in cases 7 and 10, in whom section of the right lumbar sympathetic nerves was performed, showed markedly diminished pulse deflections, the mean value being 1.1 and the maximum 3.5 cu. mm. It is important to note that the volume of the pulse deflections was increased by heat in the toes of patients with intact sympathetic innervation and reduced by heat in the toes of those subjected to section of the ipsilateral lumbar sympathetic nerves.

All patients had normal pulse deflections in the finger tips. The reactions to cold (vasoconstriction) and to heat (vasodilatation) were normal. The patients on whom section of the lumbar sympathetic nerves was performed had a volume of the pulse deflections in the finger tips which was less than normal but reacted normally to heat.

In case 10 there was occlusion of the right anterior tibial artery by an arterial embolus before the last tracing was made. There were no measurable volume deflections in the tip of the right second toe except for gamma deflections of small magnitude.

Comment.—The mechanisms for the decrease in the volume of the pulse and alpha deflections immediately following ligation are unknown. Previous studies¹⁴ indicated that the influence of venous pressure per se resulted in marked distention limiting further distensibility of the peripheral vessels. This is an important contributing factor which reduces the volume of the deflections. The fact that section of the unilateral sympathetic nerves resulted in ipsilateral increase in the volume of the pulse deflections indicates arteriolar spasm and vasoconstriction in other vessels under sympathetic control as another important factor concerned with the small pulse deflections following

13. The normal value for the volume of pulsation of the finger tip is 6.9 cu. mm., with a maximum of 12.4 and a minimum of 2.1, and for that of the toe tip the mean value is 4.0 cu. mm., with a maximum of 11.5 and a minimum of 0.7. (Burch, G. E.; Cohn, A. E., and Neumann, C.: A Study by Quantitative Methods of the Spontaneous Variations in Volume of the Finger Tip, Toe Tip and Postero-Superior Portion of the Pinna of Resting Normal White Adults, *Am. J. Physiol.* **136**:443-447, 1942).

14. Burch, G. E.; DeBakey, M., and Sodeman, W. A.: Effect of Venous Pressure on Volume Pulsation, *Proc. Soc. Exper. Biol. & Med.* **42**:858-861, 1939. DeBakey, M.; Burch, G. E., and Ochsner, A.: Effect of Chemical Irritation of Venous Segment on Peripheral Pulse Volume, *ibid.* **41**:585-590, 1939.

mean pressure four years after ligation was 253 mm. of water in the right foot and 247 mm. in the left, whereas the mean values for all initial determinations were 337 mm. in the right foot and 342 mm. in the left. In the patients followed for shorter periods there was a decline in the venous pressure in most instances. In some subjects the venous pressure fell and then rose to or above the initial value; at times the rise was followed by a second decline.

The venous pressure in the antecubital veins remained within normal limits. The low value of 26 mm. of water in case 4 is probably due to an error.

The venous pressure in the superficial abdominal veins was determined in 6 patients. In 1 the values were within normal limits (case 6), while in the other 5 the pressures were markedly elevated (table 1), reaching 254 mm. of water in 1 instance (normal values, 80 to 110 mm. of water).

Comments.—From the venous pressures obtained it is obvious that the degree of effective venous obstruction resulting from ligation of the inferior vena cava is variable. For example, in case 8 the venous pressure in the dorsal vein of the left foot was greater than 600 mm. of water, while in case 10 it was within normal limits. Such a variation indicates either a good venous collateral return in the patient in case 10 and a poor return in the patient in case 8 or incomplete ligation in the former. However, autopsy revealed a complete ligation in the patient with a normal pressure. The notable variations in local venous hypertension following ligation are most probably the result of variations in collateral venous circulation. This concept is further supported by the fact that the venous pressure in the left foot of the patient in case 8 was greater than 600 mm. of water while at the same time it was 462 mm. in the right foot. Such a difference cannot be due to incomplete ligation of the vena cava. The same sort of bilateral variations is well illustrated in case 2. The reasons for these differences in collateral circulation remain unknown. Such factors as duration and extent of the thromboses and inflammation must be of some importance. Section of the lumbar sympathetic nerves did not influence the venous pressure.

The paucity or even absence of edema (tables 1 and 6) in the lower extremities even with considerable elevations in venous pressure makes it necessary to reevaluate the role of hydrostatic pressure in edema formation. This is particularly true in congestive heart failure, in which the elevation in venous pressure is usually relatively small and the degree of edema pronounced. It is well to note that patients who had edema immediately after ligation became clinically free of it in the presence of continued extreme venous hypertension and even when

comfortable environment or in a hot and humid one, the rate of water loss increasing under the latter conditions.

* *Comment.*—The lack of disturbances in water loss in the comfortable environment shows that the circulatory disturbances associated with ligation of the vena cava do not greatly influence the diffusion of water through the skin of the legs. Likewise, the sweat function associated with thermal regulation is not changed materially, if at all, by ligation of the vena cava. These factors further indicate the relatively unimportant rôle played by hydrostatic intravascular pressure per se on the rate of diffusion of water through the skin or on the volume of sweat produced during periods of acute thermal regulation. They have even greater

TABLE 3.—Rate of Water Loss (cu. mm. per 15 Minutes per 10 sq. cm. of Surface Area) Through the Skin of Five Patients Following Ligation of the Inferior Vena Cava

Case	Date of Measurement	Right Index Finger		Right Second Toe		Right Leg		Right Forearm	
		CT *	HH *	CT *	HH *	CT *	HH *	CT *	HH *
1	4/11/42	50.2	149.0	18.8	39.5	11.2	63.0
2	5/20/42	21.6	98.7	7.7	30.1	11.0	30.6
	6/24/42	15.6	69.0	10.2	25.2	10.0	31.2
3	5/22/42	16.5	30.8	13.0	16.9	9.8	16.0
	3/ 9/43	20.7	53.5	9.8	23.7	4.6	12.6
4	5/20/42	15.5	27.7	6.9	19.5	18.0	38.2
	6/30/42	17.4	31.8	6.1	12.8	6.6	28.0
	11/ 7/42	24.7	28.0	13.5	17.6	10.0	27.2
5	6/ 1/42	13.7	24.5	12.1	19.3	10.8	23.6
	11/10/42	21.7	56.3	12.3	30.9	13.6	29.8
Mean.....		21.8	56.9	11.0	23.6	11.1	31.4	10.0	29.0
Maximum.....		50.2	149.0	18.8	39.5	18.0	38.2	13.6	63.0
Minimum.....		15.5	27.7	6.1	16.9	6.6	27.2	4.6	12.6
Normal Values									
Mean.....		23.2	47.9	12.5	31.1	8.3	32.1	4.4	25.9
Maximum.....		41.3	52.1	15.7	48.7	13.6	37.6	8.4	37.8
Minimum.....		14.0	21.7	10.4	21.8	4.1	22.4	2.0	14.0

* CT indicates comfortable room temperature and humidity and HH hot and humid room temperature.

significance when compared with the decided reduction in the rate of sweating noted previously¹⁷ in chronic congestive heart failure.

PLASMA PROTEIN

The plasma protein content was determined in 7 patients at varying intervals after ligation.

Results.—The results are summarized in table 4. There was a tendency for the plasma protein content to increase after ligation of the

17. Burch, G. E.: The Rate of Water Loss from the Skin of Patients in Congestive Heart Failure in a Subtropical Climate, *Am. J. M. Sc.* **211**:181-188, 1946.

Results.—The results are summarized in table 2. In the main, there was a tendency for the volume of the pulse and alpha deflections to be small immediately after ligation. This increased in magnitude as time progressed (table 2). Initially, the volume of the pulse deflections in

TABLE 2.—*Volume of the Pulse Deflections (cu. mm. per 0.4 cc. of Part) in the Tips of the Finger and Toes in Eleven Patients Following Ligation of the Inferior Vena Cava*

Case	Date	Right Index Finger			Right Second Toe			Left Second Toe		
		CT *	C *	H *	CT *	C *	H *	CT *	C *	H *
1	4/11/42	3.5	0.3
2	5/20/42	4.0	0.5
	6/24/42	11.0	1.2
3	5/22/42	6.9	3.5
	3/ 9/43	2.1	0.8
	3/ 6/46	2.5	1.0	4.0	0.8	0.4	3.1	0.5	0.3	3.1
	10/18/46	7.3	3.4	2.1
4	4/20/42	8.9	1.2
	6/30/42	10.3	2.7
	11/ 7/42	10.1
	2/12/46	7.0	3.0	3.1
5	5/ 7/42	4.1	0.4
	6/ 1/42	7.5	6.0
	11/10/42	9.9	5.6
	3/20/46	6.4	0.9	7.3	5.2	2.1	8.3	5.2	2.1	8.3
	10/15/46	2.1	2.2	2.2
6	2/27/46	6.4	2.1	10.0	3.3	1.5	4.5	3.3	1.5	4.5
	10/21/46	10.0	5.2	4.6
Mean.....		6.7	1.3	7.1	2.7	1.4	5.3	3.0	1.3	5.3
Maximum.....		11.0	2.1	10.0	6.0	2.1	8.3	5.2	2.1	8.3
Minimum.....		2.1	0.9	4.0	0.3	0.4	3.1	0.5	0.3	3.1
7	2/20/46	2.1	0.6	6.6	2.7	2.2	2.2	1.1†	0.2†	2.2†
	4/29/46	5.5	...	5.5	3.9	...	3.7	0.9†	...	3.7†
	6/12/46	3.1	1.3	0.5†
	10/15/46	3.0	1.0	0.5†
8	2/ 6/46	2.5	...	6.2	2.7	...	2.6	2.7	...	3.3
	5/ 2/46	6.2	5.3	6.6
	10/15/46	5.8	1.9
9	5/25/46	2.8	2.1	2.1
	6/ 3/46	3.1	3.5	2.8
	10/18/46	6.8	4.2	5.0
10	4/ 3/46	4.4	8.3	0.1†
	4/10/46	1.4	5.6	3.5†
	5/11/46	0.3	0	0.7
11	10/18/46	4.3	3.2	3.2
Mean.....		3.7	0.6	6.1	3.5	2.2	2.8	3.9	...	3.3
Maximum.....		6.8	...	6.6	8.3	...	3.7	6.6
Minimum.....		1.4	...	5.5	1.0	...	2.2	2.1
Mean.....		1.1†	0.2†	2.9†
Maximum.....		3.5†	...	3.7†
Minimum.....		0.1†	...	2.2†

* CT indicates comfortable room atmosphere; C, cool room atmosphere, and H, hot room atmosphere.

† These values were obtained in the extremity with a unilaterally intact sympathetic nervous system (consult text).

the toe tips was reduced to a mean value of 1.2 cu. mm. per 5 cc. of part in the patients with an intact sympathetic innervation. This value increased over a period (up to four years) to mean values of 2.7 cu. mm. for the tip of the right toe and 3.0 cu. mm. for the tip of the left. These

as a mean, with a maximum of 40 and a minimum of 11. For the pretibial area the mean value is 37.1 mm., the range being between 54 and 18.¹⁸ In the only determination made on the volar surface of the forearm the value was found to be normal. In the pretibial areas the mean values were found to be 42 and 50 mm. of water for the right and left sides respectively. These mean values are at the maximum limit of normal for the pretibial area, thus indicating a rise in tissue pressure following ligation of the vena cava. There was a tendency for the magnitude of the tissue pressure in the pretibial areas to vary directly with the degree of the venous hypertension. The level of the tissue pressure varied inversely with the degree of edema in the lower extremities.

Comment.—The elevation of tissue pressure following ligation indicates the role of hydrostatic pressure of the tissues in limiting edema formation. The relative significance of this factor among the many

TABLE 5.—*Subcutaneous Tissue Pressure (Millimeters of Water) in Six Patients Following Ligation of the Inferior Vena Cava*

Case	Date	Arm	Right Leg	Left Leg
3	10/18/46	..	46	40
5	5/ 7/42	26	..	86
	10/15/46	..	28	28
7	10/15/46	..	30	45
8	10/15/46	..	58	58
9	10/18/46	..	58	56
11	10/18/46	..	30	36
Mean.....		26	42	50
Maximum.....		..	58	86
Minimum.....		..	28	28

other factors concerned with edema formation is not known. Previous studies¹⁸ have indicated the importance of tissue pressure in edema formation, in which the former became progressively more significant as edema increased in magnitude.

CLINICAL OBSERVATIONS

Clinical observations consisted of the elicitation of a thorough history and physical and laboratory examinations, with frequent follow-up examinations in the postoperative period. Only pertinent findings are reported.

A. *Functional Capacity of Lower Extremities.*—There was no diminution in functional capacity either generally or locally. All the patients were able to do their usual duties without discomfort of any sort. There was no claudication.

B. *Edema.*—The results of the observations on edema are summarized in table 6. Edema was present in all patients except 2 (cases 9

ligation of the inferior vena cava. With the passage of time, there is a tendency for the volume deflections to return to within the normal range in spite of the fact that the venous hypertension persists. This suggests a decrease in vasoconstrictor tone in subjects with an intact sympathetic innervation.

The data were insufficient to test adequately for a correlation of the volume of the pulse deflections to the degree of edema, the degree of venous hypertension and the state of the sympathetic innervation.

The fact that the magnitude of pulse deflections decreased further when the room atmosphere was made cool and increased when the atmosphere was made hot indicated continued sympathetic and vasoconstrictor control of the peripheral blood vessels in the presence of obstruction of the vena cava and considerable venous hypertension. These responses were altered by section of the lumbar sympathetic nerves (table 2).

The embolic occlusion of the right anterior tibial artery of the patient in case 10 resulted in a disappearance of the pulse and alpha deflections in the right second toe. The slow but persistent gamma deflections indicated slow but definite shifting of blood in and out of the parts supplied by that artery. These shifts were probably of great significance in the maintenance of tissue nutrition, because there was only a superficial loss of tissue. The quantitative nature and significance of these shifts have not been fully evaluated. Their importance should be borne in mind.

RATE OF WATER LOSS

The rate of water loss from the right index finger tip, right second toe tip, right pretibial area and the volar surface of the right forearm was measured quantitatively by a method previously described.¹⁵ The rate of water loss was determined for two successive fifteen minute periods, with an environmental temperature of 75 F. plus or minus 1 and a relative humidity of 50 per cent plus or minus 3. The room temperature was raised to 100 F. plus or minus 1 and the humidity to 75 per cent plus or minus 2 and measurements made for another two successive fifteen minute intervals. The rate of water loss was determined for 5 patients (cases 1 to 5).

Results.—The results shown in table 3 were previously described.⁶ The normal values for the rate of water loss had been established previously.¹⁶ There were no significant disturbances in water loss in a

15. Neumann, C.; Cohn, A. E., and Burch, G. E.: A Quantitative Method for the Measurement of the Rate of Water Loss from Small Areas with Results for Finger Tip, Toe Tip, and Postero-Superior Portion of the Pinna of Normal Resting Adults, *Am. J. Physiol.* **132**:748-756, 1941.

16. Burch, G. E., and Sodeman, W. A.: Regional Relationships of Rate of Water Loss in Normal Adults in a Subtropical Climate, *Am. J. Physiol.* **138**: 603-609, 1943.

were dilated and formed an unusually prominent network. In a few instances the superficial abdominal veins were moderately tortuous. The direction of blood flow was invariably cephalad in these veins of the trunk.

F. Miscellaneous.—The skin of the legs and feet presented no abnormal pigmentation, cyanosis, mottling or discoloration of any sort. There was no change in the texture or thickness of the skin. Sensation to heat, cold, touch and pain remain undisturbed. There were no ulcerations or infections of the skin.

Comment.—The fact that the extremities failed to reveal clinically any change in function or in character of the skin or any discoloration, anatomic changes in the veins or neurologic dysfunction certainly indicates the adequacy of the compensatory readjustments following ligation of the inferior vena cava.

GENERAL COMMENT

The rather remarkable circulatory readjustments which occurred in the lower extremities of patients studied after ligation of the inferior vena cava are of considerable clinical importance. It is because of such adjustments that the surgeon can ligate the inferior vena cava, with the resultant sustained venous hypertension, without producing demonstrable detrimental effect. Needless to say, the ligation must be below the entrance of the renal veins. One of the most interesting adjustments is that concerned with the exchange of water between the intravascular and extravascular spaces. The fact that edema does not develop at all or develops to only a slight extent indicates the relatively unimportant role of hydrostatic intravascular pressure per se in edema formation. As long as only the hydrostatic pressure is increased, compensatory mechanisms develop to a high degree. It is such compensatory mechanisms which remain unknown and which deserve considerable study. The failure of edema to develop in the presence of a venous pressure of 400 mm. of water or more must cast doubt on the concepts presented to explain the edema in congestive heart failure on the basis of increased hydrostatic pressure.

The development of collateral circulation can be rapid and efficient. In 1 patient the pressures in the veins of the feet were normal soon after complete ligation of the inferior vena cava. This collateral circulation must be developed through the abdominal, gluteal, retroperitoneal, pelvic and hemorrhoidal veins.

The development of collateral circulation in these veins has been discussed by O'Neil.^{4b} The ovarian veins are not concerned with collateral circulation in the patients reported on here since they were ligated along with the vena cava. The lymphatic system must play an

vena cava. Although a rise did not occur in 3 of the 7 patients, relatively high values were reached in 2. The patient in case 3, with a total plasma protein level of 5.6 Gm. per hundred cubic centimeters, had persistent vomiting for four months, with a loss of 28 pounds (12.7 Kg.) in body weight. The patient in case 5 likewise had repeated vomiting for two months prior to the last determination. The patient in case 7 was on a self-imposed carbohydrate reduction diet for two months before Oct. 15, 1946.

Comment.—The significance of the tendency toward hyperproteinemia following ligation can only be conjectured. The relatively small number of patients studied makes the importance of the findings difficult to interpret. It is possible, however, that body mechanisms are so disturbed by the venous ligation that hyperproteinemia might be expected to

TABLE 4.—*The Plasma Protein Content (Grams per Hundred Cubic Centimeters) in Seven Patients Following Ligation of the Inferior Vena Cava*

Case	Date	Albumin	Globulin	Total
3	10/18/46	4.3	1.3	5.6
5	3/20/46	6.9	3.7	10.6
	10/15/46	4.1	2.3	6.4
6	10/21/46	5.9	1.8	7.7
7	4/29/46	5.1	3.2	8.3
	6/13/46	3.3	3.4	6.7
	8/12/46	4.8	3.5	8.3
	10/15/46	3.3	2.0	5.3
8	5/ 2/46	4.3	3.4	7.7
	10/15/46	4.4	2.3	6.7
9	10/18/46	6.7	2.7	9.4
11	10/18/46	3.9	1.9	5.8
Mean.....		4.8	2.6	7.4
Maximum.....		6.9	3.7	10.6
Minimum.....		3.3	1.3	5.3

result. The hyperproteinemia could be an important factor in limiting the degree of edema formation through its influence on intravascular oncotic force. More data are necessary to support claims that such adjustments are compensatory.

TISSUE PRESSURE

Measurements of the pressure in the subcutaneous tissue in the pretibial area were made in 6 patients at varying intervals after ligation by a direct method previously described.¹⁸ All measurements were done with the part at heart level.

Results.—The results are shown in table 5. The normal value for tissue pressure in the volar surface of the forearm is 23.6 mm. of water

18. Burch, G. E., and Sodeman, W. A.: The Estimation of Subcutaneous Tissue Pressure by a Direct Method, *J. Clin. Investigation* **16**:845-850, 1937.

Clinical observations revealed normal function of the lower extremities and normal texture, temperature, color and response to sensation of the skin. The veins of the feet and legs were small; varicosities were limited to minute veins of the skin. The abdominal veins were dilated, and the blood flow was cephalad. Edema occurred in all but 2 patients and disappeared early in convalescence in all except 2 in whom the edema was present for eight months.

Clinical and physiologic observations failed to reveal any detrimental effect from ligation of the inferior vena cava. The circulatory adjustments were adequate, although not all the compensatory mechanisms are clearly understood.

and 10), in whom there was no edema either before or after the operation. The severity of the edema varied from mild to extreme among the 10 patients. It disappeared within two months after operation except in 3 patients. In several instances there was no clinical edema by the end of the third week. This disappearance of the edema occurred without a concomitant fall in venous pressure (tables 1 and 6). In only 2 patients did the edema persist for as long as eight months (cases 4 and 7). In case 4 the nature and behavior of the edema could not be properly evaluated since it was complicated by congestive heart failure during convalescence. Section of the sympathetic nerves had no influence on the occurrence, degree or disappearance of the edema.

C. *Skin*.—The temperature of the skin was noted by palpation and in a few instances by means of thermocouples. It remained within normal

TABLE 6.—*State of Edema in Twelve Patients Following Ligation of the Inferior Vena Cava*

Case	Course of Edema
1	Mild degree of edema in both legs for three weeks postoperatively; no edema after three weeks
2	Marked edema in both legs for several weeks; little edema eight weeks after operation
3	Edema severe in the right leg and moderate in the left for three weeks after operation; further observations revealed no edema
4	Considerable edema bilaterally for eight months after operation and then edema disappeared; congestive heart failure developed during convalescence
5	Slight bilateral edema two weeks after operation; no edema four weeks post-operatively or since that time
6	Edema more pronounced in the left leg; at the end of six weeks all edema was gone, and it has not appeared since that time
7	Edema of the left leg before operation; postoperatively, both legs were extremely edematous and at the last observation, eight months postoperatively, there was moderate edema of both legs
8	Slight edema for two months and none thereafter
9	No edema at any time
10	No edema at any time
11	Moderate edema at the last observation, four months after operation
12	Slight edema on the second postoperative day; patient died early after operation

limits. In the 2 patients in whom section of the unilateral sympathetic nerves was performed (cases 7 and 10) the leg on which partial sympathectomy had been performed was warmer than the opposite one.

D. *Nails*.—The toe nails did not change in rate of growth or in appearance after ligation of the inferior vena cava.

E. *Veins*.—The large veins of the legs and feet were not dilated. Indeed, one was impressed by the fact that the veins were smaller than would be expected normally. There were some small varicosities of the small veins of the skin, with an occasional rupture, in 4 patients. The extent of the varicosities was slight in 2, moderate in 1 and severe in another. However, there were no demonstrable varicosities in the large superficial veins of the lower extremities. The superficial veins of the abdominal wall and gluteal region and also the long thoracic vein

PATHOLOGY

Here will be described the pathologic processes leading to obstruction of the hepatic veins and the resulting hepatic changes.

Venous Lesions.—There are three main sites for obstruction. It may occur in the inferior vena cava, in the ostiums of the hepatic veins or in the hepatic veins themselves. It is often difficult to determine whether the thrombosis occurred primarily in the vena cava or in the ostiums of the hepatic veins. In 5 cases the block was due to neoplasm in the cava; in 2 of these the condition was reported as endothelioma (Hallock and others and Unruh) and in 3 as hypernephroma (Armstrong and Carnes; Jacobson and Goodpasture, and Weber). In 20 cases there was thrombosis of the cava—a rare lesion. Block of the upper part is extremely rare. Only 3 to 4 per cent of Pleasants' patients with thrombosis of the inferior vena cava had a thrombus in the upper third of the vessel. In 18 other cases there was mural thrombosis or intimal thickening without block.

In many cases the ostiums of the hepatic veins appear to be the initial site of the block; even when there is extensive thrombosis, scarring is frequently most severe and evidently of longer duration at this site. There remain a number of cases in which the ostiums are free, the most profound changes being in the hepatic veins themselves. Recently, authors have stressed lesions in the walls of the vessels. These are discussed in the section on etiology.

Liver.—The lesions found in the liver depend on the duration of the thrombosis. In the acute stage there is severe venous engorgement, resulting in central lobular necrosis of hepatic cells. Later cirrhotic change develops, and nodular regenerative hyperplasia is common. Old and recent lesions are frequently found side by side in the same liver, confirming the clinical suggestion that numerous acute attacks of thrombosis are common.

In 3 cases (Nishikawa and Hutchison and Simpson) there developed primary carcinoma of the liver. There seems no doubt that this was the true interpretation, and it would appear reasonable to suggest that the carcinoma supervened on regenerative hyperplasia, as occasionally occurs in portal cirrhosis. An enlarged caudate (spigelian) lobe is frequent, as was noted by Nishikawa. It is probable that the thrombotic process misses the usually separate hepatic vein supplying this lobe, enabling compensatory hypertrophy to occur more readily.

Other Lesions.—Thrombosis of the portal veins is a rare and usually terminal event. In 2 cases there developed an infarction of the intestines. The only other intestinal lesion noted is a varying degree of congestion. Apart from the vascular lesions mentioned in the next section, the changes described in the spleen are those of severe venous engorgement.

important part in limiting edema formation. Follow-up studies of the patients for as long as four and one-half years in some instances failed to reveal any clinical benefits from section of the sympathetic nerves. There was no difference in edema formation when section of the sympathetic nerves was performed and when it was not performed. The differences observed were limited to warmer extremities on the side subjected to section of the sympathetic nerves as well as the presence of greater volumes of the pulse deflections. In spite of this no evidence of over-all clinical benefit could be detected. It is possible that in certain circumstances, not observed in any of these cases, section of the sympathetic nerves might be advantageous.

SUMMARY AND CONCLUSIONS

Twelve female patients in whom the inferior vena cava was ligated for pelvic thrombophlebitis were studied for a period of up to four and one-half years. The methods of investigation were described and the results correlated with the clinical state of the patient.

After ligation of the inferior vena cava the pressure in the dorsal pedal veins was markedly elevated in all but 1 patient; the values ranged from 120 to over 600 mm. of water. A gradual fall in venous pressure occurred with time, but the maximum normal limits were reached in only 2 instances. There was no relation of venous pressure to the degree of edema or to section of the sympathetic nerves. The pressures in the antecubital veins were normal. Five of 6 patients studied had an elevated venous pressure in the superficial abdominal veins; values ranged from 60 to 254 mm. of water.

The volume of pulse deflections in the toe tips was reduced immediately after operation to a mean value of 1.2 cu. mm. per 5 cc. of part, which increased with time to mean values of 2.7 and 3.0 cu. mm. Section of the sympathetic nerves resulted in a greater mean value (3.5 cu. mm.) immediately after operation.

Five patients had a normal rate of water loss from the finger tips, volar surface of the forearm, pretibial area and toe tip in a comfortable environment, and the rate increased normally in response to a hot and humid environment.

The plasma protein levels tend to be slightly higher than normal, with mean values of 4.8 Gm. of albumin, 2.6 Gm. of globulin and 7.4 Gm. of total protein per hundred cubic centimeters. The range for total protein was 5.3 to 10.6 Gm., for albumin 3.3 to 6.9 Gm. and for globulin 1.3 to 3.7 Gm.

After ligation of the inferior vena cava, tissue pressure in the pretibial areas bilaterally rose to mean values of 42 and 50 mm. of water respectively. Tissue pressure tended to vary directly with the venous pressure and inversely with the degree of the edema.

tonitis leading to periphlebitis, as postulated by Mann and Hall and Frerichs, is excluded in all but their cases by the absence of any peritoneal reaction except the mild one so common in long-standing ascites. Venous block by gumma was reported by Fagge, West and Wilks; however, gummas of the liver are now extremely rare, and in all recent cases syphilis can be ruled out by a negative reaction to the Wassermann test. Hart reported an instance of death resulting from treatment with arsphenamine in which miliary granulomas were found around the small hepatic veins and suggested that such lesions might give rise to thrombosis of the hepatic veins. It appears likely that these lesions were really those of a necrotizing arteritis due to hypersensitivity to the arsenical compound. Hart's concept, however, is interesting, and further remarks about general vascular disease as a cause will be made in this article.

Terminal thrombosis related to hepatic suppuration is recorded by Winternitz and Visconti and also occurred in a case in the Massachusetts General Hospital. While this condition is of pathologic interest, it is terminal and is of no clinical interest.

Thompson and Turnbull suggested that eddying of the streams of blood at the junction of the hepatic veins with the vena cava might explain the many cases in which the thrombosis occurred at the ostiums of the hepatic veins; marked obliquity of the entering veins is a possible added factor. It is generally accepted that at the site of alterations in caliber or at the confluence of blood streams deposition of cells and fibrin may occur on the walls of vessels. The authors remarked that such changes are extremely rare at the ostiums of the hepatic veins, but they reported a case in which there was a projecting ledge of thrombus at the venous junction, just where the main block so often occurs in the Chiari syndrome. There seems no doubt that this theory adequately accounts for the great frequency of thrombosis at the hepatic vein ostiums, but other factors must be present to a greater or lesser degree.

Also among general causes for the syndrome must be placed diseases in which there is a well recognized tendency toward thrombosis. There are in the literature 8 cases of polycythemia vera in which the syndrome occurred (Altschule and White, Baehr and Klemperer, Berk, Cole, McAlpin and Smith, Oppenheimer and Ulhorn). Relation of the onset of the illness to pregnancy has been noted four times (Chiari's case 1, Coronini and Oberson's case 8, Lange's case and Nagayo's case 3). I have recently observed a case of leukemia in which thrombosis of the veins of the right lobe of the liver had occurred.

A further probable cause is phlebitis of the hepatic veins, with cellular infiltration of the media, intimal thickening and superimposed thrombosis. Hess, Meyer, Ohno, Pacher and Satke brought forward

THROMBOSIS OF THE HEPATIC VEINS

The Budd-Chiari Syndrome

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IT IS THE purpose of this paper to report 2 cases of thrombosis of hepatic veins and review 95 from over 100 in the literature, to emphasize that the syndrome is not always due to one disease process, as is so commonly implied, and to attempt to give a clearer conception of the various other processes which may cause it.

In the majority of reported cases there is gross obstruction of hepatic veins, leading to engorgement and necrosis of the liver and to portal obstruction. In some instances the block occurs as a final episode in an already advanced disease which itself masks the characteristic clinical picture of the Chiari syndrome or leaves no time for its development. There is also a smaller group of cases in which the obstruction is limited to one lobe or to part of a lobe. While there is a pathologic unity which may be expressed by referring to all cases as examples of thrombosis of the hepatic veins, it is felt that descriptive separation is necessary. It is proposed that the name "Chiari" or "Budd-Chiari" syndrome should be retained for cases in which there is gross blockage of the hepatic veins and that cases with more limited lesions, not giving the full picture, should be referred to simply as cases of thrombosis of the hepatic veins. While this paper is primarily concerned with the Chiari syndrome, remarks concerning etiology and pathology cover the minor group also. Two previously accepted cases have been excluded. The patient in Sternberg's second case had thrombosis of the vena cava, but the upper part of the vessel was free, as apparently were the hepatic veins; reference is made only to a fatty liver. In Hoover's second case the diagnosis appears doubtful, and there was no autopsy.

Some reviews deserve special mention. These are the original paper by Chiari, an excellent review of the older literature by Hess, the paper by Thompson and Turnbull, the comprehensive article by Nishikawa containing a report of 10 cases and, more recently, the articles of Satke and Coronini and Oberson.

From the Royal Victoria Infirmary.

Splenic Enlargement.—Enlargement of the spleen is not nearly so frequently noted clinically as is hepatic enlargement. It is not usually gross, extending as a rule about a fingerbreadth below the costal margin. In only 1 atypical case was it of considerable degree.

Venous Collaterals.—The presence of venous collaterals is one of the most important signs. Usually the enlargement is over the upper part of the abdomen and the lower part of the thorax, especially near the xiphoid cartilage, where anastomosis between the superior epigastric, medial xiphoid and internal mammary veins takes place; only a few reports mention a caput medusae. The presence and size of these anastomotic veins are related to the duration of the thrombosis. The few reports mentioning this point suggest that a few weeks are necessary for the development of obvious dilatation. In the second case reported on here the dilatation appeared almost immediately after the thrombosis. In the early stages there may be only dusky engorgement of fine vessels, giving a cyanotic hue. Pleasants pointed out that if there was thrombosis in the vena cava the lower the thrombosis extended, the lower were the collaterals on the abdominal wall.

Edema of the Legs.—Edema of the legs was present to a greater or lesser degree in 43 cases. In many it was transient or limited to the feet. Considerable edema, especially if it extends to the thighs, should strongly suggest that the thrombosis has involved the vena cava. This statement, of course, implies exclusion of other general causes of edema.

Jaundice.—The absence of gross jaundice and the presence of the slight, latent or clinical form are the most important features. Reports vary in their statements on this point, some denying the presence of jaundice, others referring to subicterus. In the few cases in which detailed examination was made, mild icterus was demonstrated. The van den Bergh test has shown an increased indirect value. Six reports mention the occurrence of increased urobilin in the urine, or occasionally of bile. There is too little available information to enable definite figures to be given.

Other Evidence of Hepatic Damage.—Unfortunately, only 5 case reports refer to tests of hepatic function. Sohval mentioned low plasma cholesterol levels, with only a trace of ester fraction. Kahn and Spring noted a cholesterol level of 173.9 mg., and Goldstein a level of 166.3 mg. Satke reported negative reactions to galactose tests in 2 instances, with a positive reaction to the tetrachlor-phenolphthalein test in 1; in the latter instance scanty amounts of leucine and tyrosine were found in the urine.

Vomiting.—Vomiting is mentioned in about one quarter of the cases, usually being most severe at the time of an acute episode.

Nishikawa presented extensive charts of the venous anastomoses; these, however, appear too well known for review here.

RELATED EXPERIMENTAL WORK

Simonds and Callaway and Jergesen reported on the changes occurring in the livers of dogs after mechanical constriction of the hepatic veins for ten to fifty minutes. They found swelling and granulation of the hepatic cells, resulting later in complete sinusoidal collapse. Hyaline thrombi were found in many central and sublobular veins, and a large number of mononuclear cells were present, with some proliferation of the sinusoidal endothelium. The picture was reported as resembling the focal necrosis of typhoid. The authors emphasized the presence of lymphatic dilatation, only once mentioned as occurring in a human being (Ohno).

ETIOLOGY

Age.—The youngest patient with thrombosis of the hepatic veins mentioned in the literature is Gee's 17 month old patient. Unruh's patient was 1 year old, but in this instance the condition was due to endothelioma of the vena cava. The oldest patient mentioned was 61 years. The average in 86 cases in which age was mentioned was 34 years. Hess gave the average as 28.5 years.

Sex.—Of 88 patients for whom the sex was recorded, there were 50 males and 38 females. This does not agree with previous statements, since Byrom remarked that the condition is twice as common in females and Rolleston that the sexes are equally affected.

Predisposing Diseases.—The syndrome of thrombosis of the hepatic veins may be due to a variety of disease processes; moreover, there can be no doubt that in any one case several factors are usually active. There may be a general disease, such as polycythemia, carrying a pronounced tendency to thrombosis, which in combination with a minor local lesion will cause thrombosis of the hepatic veins. Conversely, there may be a gross local lesion with a minimal general disease. Some of these factors, both general and local, will be considered.

A congenital vascular fault may be the local factor in thrombosis occurring in early life but is not likely to be present in the majority of patients in the older age groups. The theory that there is spread of the obliterative process from the ductus venosus to the hepatic veins, suggested by Moore and Rolleston, has no supporting evidence. The presence of a congenital venous anomaly, such as a valvular fold, is a possibility but would be extremely difficult of proof. The theory of Kretz that repeated trauma, such as occurs because of the coughing in pertussis, might lead to tearing of the venous walls and to subsequent thrombosis has nothing to commend it. The diagnosis of primary peri-

Thrombosis of the portal veins presents similar features, including sudden onset with pain, ascites and the later development of anastomotic veins. The essential point of difference is the absence of hepatic enlargement and even the minor manifestations of jaundice in uncomplicated cases of portal vein thrombosis. In portal cirrhosis the clinical picture lacks the drama of thrombosis of the hepatic veins. Jaundice if present either will be or will become more pronounced than it is in the Chiari syndrome. The history of a case of cirrhosis is frequently suggestive of the diagnosis, and the age incidence is rather different. Confusion with carcinomatous or tuberculous peritonitis and with adhesive pericarditis is not likely.

PROGNOSIS

The duration is variable, but, as Thompson and Turnbull stated, there are two main groups. In the majority of cases the disease is of short duration, in some lasting only a few days. In the smaller group the disease may last from ten to twenty-eight years. Even in this type, however, there is often a story of a recent sudden episode. Chiari's second case is a good example of this, and examples will also be found in Rolleston's discussion in the paper by Hoover and in the paper by Hutchison and Simpson.

TREATMENT

The treatment of this disease unfortunately does not offer much scope for discussion. It must be on the same lines as the treatment for portal cirrhosis. Byrom's suggestion that paracentesis accelerated death does not appear correct. One gathers that the few patients who did die after tapping were extremely ill before the operation. One point of great importance is that, although this is an extremely fatal disease, patients may live for many years before succumbing, perhaps to a fresh thrombosis. There is no doubt that the fatal termination can be greatly accelerated by operative intervention. Of 9 patients who were operated on, 8 died, the majority within two to three days and 2 within twelve hours.

REPORT OF CASES

CASE 1.—*Clinical History*.—The patient was a miner 31 years of age. He had been in good health all his life, apart from occasional bouts of abdominal pain and diarrhea, until three weeks before his admission to the hospital. He went to work one morning feeling well, but during the day he began to have such severe pain in the abdomen that he was obliged to return home, and by the evening he felt so ill that he had to retire to bed. On attempting to dress the following morning, he found his abdomen so swollen that he was unable to put on his trousers. During the period prior to his admission, the swelling progressed more slowly. After the first few days, pain was not so prominent. There was no vomiting or diarrhea, and his appetite was good.

strong evidence of this. There seems no doubt that in certain cases it is one of the main local factors leading to thrombosis of the hepatic veins.

Coronini and Oberson expressed the most interesting view, that thrombosis of the hepatic veins can result from a general vascular disease. They found inflammatory changes in the intima of the hepatic veins of a serofibrillary character, often with well defined medionecrosis. The generalized nature of the disease is supported by the finding of similar lesions in the radicles of the portal veins and in the splenic vasculature, resulting in a "fibro-adenie" resembling that described in Banti's syndrome. More rarely the pancreas and the kidney may be affected, and the authors described tissue damage in the heart of the type seen in rheumatism. Stressing the type of the vascular lesions, they suggested a rheumatic basis for thrombosis of the hepatic veins, i. e., an allergic tissue reaction in the sense of Klinge and Rossle.

CLINICAL FEATURES

Abdominal Pain.—Usually pain is the initial symptom. It precedes hepatic enlargement and ascites and is one of the most constant features. It differs in severity, varying from mild discomfort and "indigestion" or a sense of pressure to a severe cramping pain. It is usually epigastric, with predominance under or over the right costal margin, and sometimes radiates to the back and the loins. Some reports mention the occurrence of attacks of pain for years before the final illness, but it appears likely that these represent minor episodes of thrombosis. Sudden stretching of its capsule by the engorged liver substance would appear to be the explanation of the pain.

Ascites.—Large quantities of transudate, occasionally hemorrhagic and rapidly recurring after paracentesis, are usually found. In 5 cases ascites was absent clinically, but in 3 of these it was found at autopsy or on laparotomy. In 1 case death occurred at five days, and there may not have been time for an ascitic collection to develop. It is to be assumed that the development of an adequate collateral circulation is the explanation, and it is of interest that in several cases in which there had been earlier gross ascites there was little fluid at autopsy.

Hepatic Enlargement.—Hepatic enlargement is usually striking, but difficulty in palpation is frequent owing to massive ascites. However, the organ is generally readily palpable after paracentesis. A rapid, tender enlargement is usual, extending as a rule to two or three finger-breadths below the costal margin. In cases in which the disease is of longer duration, the edge recedes, tenderness passes off and the organ becomes harder as cirrhotic changes develop. It is usually smooth and firm, but in a few cases irregular masses due to primary or secondary carcinoma of the liver have been palpable.

fluid. The visceral and parietal peritoneum and the intestines were a dusky red from considerable dilatation of large veins, closely set venules and capillaries. The parietal pleura showed the same engorgement, but the pleural sacs contained no fluid. In the subcutaneous tissues of the lower part of the chest there were many dilated venules. The pectoral muscles showed similar changes, and in addition there were numerous dilated veins. The internal mammary veins were slightly dilated; seven trunks were present. The azygos vein was dilated, having a diameter of 1.5 cm. There was no evident caput medusae, but there were well marked attempts at a collateral circulation in the usual sites. In the pericardium and anterior mediastinum there were many dilated veins and capillaries. The superior vena cava had a circumference of 6.0 cm. just before entering the auricle; the innominate veins were not obviously dilated. The right side of the heart was much dilated; however, beyond a little myocardial scarring there was nothing remarkable. The inferior vena cava showed a vestigial valve 5.0 cm. long and up to 1.5 cm. broad; at 6.0 cm. below the diaphragm the vessel was 8.0 cm. in circumference. There were no thrombi present. The ostiums of the hepatic veins seemed smaller than normal, and one of the superior group had protruding from it a piece of antemortem clot 0.6 cm. long. The liver appeared reduced in size but weighed 1,650 Gm. The right lobe had a finely granular and wrinkled exterior and was dark bluish. On section its lateral half showed occlusion of practically all the hepatic veins by recent, or at least recently organized, thrombi. In the medial portion practically all the hepatic veins were filled by pale, firm, organized thrombi; in some, recanalization was apparent to the naked eye. Recent thrombi were infrequent.

The liver itself was a dark plum color and was firm. Lobular markings were usually not made out; when they were, they indicated small lobules. The appearance was that of so-called red infarction. In the lateral portion were a few scattered yellowish foci of "normal" liver, 0.2 cm. or so in diameter. Springing from the under surface of the right lobe, some 5.0 cm. from its right margin, was an irregular tubular mass of accessory hepatic tissue. It had a rounded termination and constituted one third to one half of the liver mass, measuring 12 by 10 by 6 cm. Its line of demarcation from the rest of the right lobe was irregular but sharply defined. Unlike the other lobes, it was covered by a smooth thin capsule, had a yellowish color and was extremely soft.

The left lobe was reduced in size, being only 2.5 cm. long and 5.0 cm. broad. Its external appearance resembled that of the right lobe, but one third of it was occupied by a pale, depressed, scarred, triangular area. On section most of it resembled the medial portion of the right lobe, but the triangular scarred area contained only a few recognizable vessels and no hepatic cells.

Microscopically the hepatic veins, particularly the large trunks, showed thrombi of varying ages. Some were recent, although even these were organized. Others were old and fibrosed, and in these channels of recanalization often showed recent thrombi. Inflammatory changes were not evident. Hepatic tissue in the distribution of the thrombosed veins had disappeared, apart from a thin layer of cells around the portal tracts. The tracts themselves showed an increase of fibrous tissue, and early bile duct proliferation was present near them. In the accessory lobe the lobules were enormous and large vessels and portal tracts were absent, confirming the microscopic appearance of regenerated liver. The spleen was much enlarged, weighing 640 Gm., and the sinusoids were distended by blood. There was an old infarct measuring 5 by 3 cm., with microscopically a number of smaller deep infarcts such as might arise as a result of venous lesions. The kidneys were enlarged (400 Gm.) and showed intense congestion, and there was scanty exudate in some

hematemesis is rare; in most cases it is clearly due to varicose esophageal veins. Melena or rectal bleeding is even rarer.

Diarrhea.—Only five references to diarrhea were found. In 2 cases it was diffuse and watery and may have been related to edema of the bowel wall.

Dyspnea.—Dyspnea is a frequent symptom in cases of massive ascites, being due to upward displacement of the diaphragm.

Pleural Effusion.—This is rare and usually terminal.

Neurologic Signs.—Several authors have mentioned the occurrence of a drowsy state drifting into the picture of cholemia in the terminal stages. Goldstein reported a case in which there were striatal signs. There was a masklike face, poverty of eye movements, monotonous speech, salivation, tremor of the extremities, an oculomotor palsy and left trigeminal hyperalgesia. Striatal lesions resembling those seen in postencephalitic parkinsonism were found at autopsy. This case is a further example of the interesting relation between striatal disease and hepatic damage.

Renal Damage.—Evidence of this is exceptional. Altschule and White reported a case of terminal uremia; however, even in cases of caval thrombosis there is no renal abnormality, as the thrombus is almost invariably in the upper part of the vessel.

Clinical Features of Minor Thrombosis.—The features just described apply to the classic Chiari syndrome with well defined venous block. In other cases the thrombosis is much more limited but may be repeated over years until the full clinical picture emerges. It would be well to bear in mind the diagnosis of thrombosis of the hepatic veins in the presence of obscure pain in the upper abdominal area, especially if there are even minor signs of hepatic damage and if there are points in the history which make a diagnosis of infective hepatitis unlikely. If such an incident should occur in the course of some disease in which thrombosis is common, then the diagnosis would be even more worthy of consideration.

DIFFERENTIAL DIAGNOSIS

The first correct diagnosis was made by Willcocks in 1896. Since then the syndrome has been diagnosed during life in 10 cases, including the 2 cases presented here. The great majority of cases present such a typical picture that there are not many other diseases closely resembling it. There are a few atypical cases in which diagnosis is difficult, such as the 5 in which there was no ascites and Satke's case 4 which appeared to be an instance of isolated splenomegaly. In cases in which the thrombosis occurs as a terminal event diagnosis is impossible.

the lumen of the vena cava was occupied by crisscross bands of fibrous tissue, which was due to organization of the thrombus: in the meshes were several recent thrombi. The renal veins were themselves free, but the right vein showed evidence of an old mural thrombus, and there was an old infarct in the kidney. At one point there was a slight proliferation of the intima of the renal artery. The spleen weighed 83 Gm. (normal, 37 Gm.); there was moderate pulp congestion with prominent germ centers. The esophageal veins were rather more prominent than usual, but they showed no varicosities. A small myocardial artery showed pronounced intimal proliferation, without reduplication of the elastica.

COMMENT

Case 1 clearly shows the result of repeated thromboses over a long period. The triangular area in the left lobe of the liver was evidently of long duration. The rest of the lobe and the medial portion of the right lobe had been more recently involved, and the lateral portion of the right lobe more recently still. It is interesting in this respect to recall the attacks of abdominal pain. The thrombosis had evidently occurred in the hepatic veins near the ostiums, but unfortunately all the thrombi were so old that no conclusions could be reached as to their pathogenesis. The splenic infarcts strongly suggested that there had been involvement of the veins in the spleen as well as of those in the liver; there was no evidence of vascular lesions in other organs. The possible relation of the vestigial valves to the thrombosis is of interest.

In the second case the thrombosis probably commenced about the ostiums of the hepatic veins and spread to the cava and to the hepatic veins proper. Here again the age of the thrombi obscured their pathogenesis, but support for the theory of a general vascular disease was given by the renal infarct, the nature of which suggested a venous thrombosis as the cause, and by the vascular lesion in the myocardium.

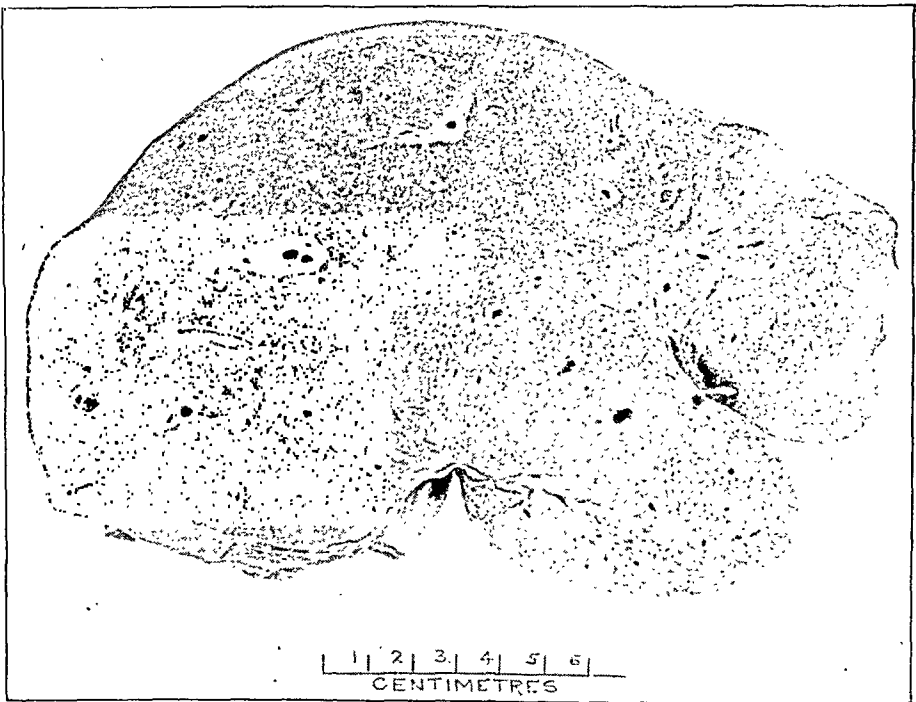
SUMMARY

Two cases of the Chiari syndrome have been reported and 95 reviewed. It is concluded that the syndrome may result from a number of disease processes, and an attempt is made to clarify these and also to define the clinical picture. It is also suggested that minor degrees of thrombosis of the hepatic veins occur and that the diagnosis should be borne in mind in cases of obscure pain in the upper abdominal area, especially when there is any evidence of hepatic damage.

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On his admission to the hospital there was gross ascites, respiration being embarrassed by upward pressure on the diaphragm. On the upper abdominal wall a few enlarged veins could be seen. After paracentesis, an extremely hard, non-tender liver could be felt, and no splenic enlargement was noted. There was no edema of the legs. Tapping was carried out three times, a total of 31 liters of pale fluid with a protein content of 1.0 per cent being removed. The liver edge receded during this period, and increasing hardness was noted. There was only slight jaundice immediately before death. No abnormal physical signs were found in the cardiovascular system, lungs or nervous system. Examination of the stools persistently revealed occult blood. The Wassermann reaction was negative. During the last few days of his illness, the patient relapsed into a comatose state, and the mode of death was that so commonly seen in severe necrosis of the liver.



Photograph of a section through the liver in case 1. To the left is the greatly engorged, recently involved right lobe. In the hepatic veins can be seen thrombi of varying ages. To the right is the mass of accessory hepatic tissue, and the large lobules are clearly shown. Above and to the right is a portion of the left lobe grossly scarred from long-standing infarction.

Several diagnoses were considered. Infective hepatitis was excluded by the absence of pronounced jaundice coupled with the presence of recurrent gross ascites. A diagnosis of cirrhosis did not seem tenable for a previously healthy man with a remarkably rapid onset of disease accompanied with pain. The hepatic enlargement made an uncomplicated portal thrombosis most unlikely. The history alone appeared to rule out the diagnosis of a neoplastic process, as did the type of peritoneal fluid. It was felt that the history and clinical findings were so strongly suggestive of thrombosis of the hepatic veins as to warrant a diagnosis of the Budd-Chiari syndrome.

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capsular spaces. The jejunum was edematous and intensely congested, as were the ileum and large intestine.

CASE 2.—Clinical History.—A previously healthy girl of 2 years of age took ill suddenly a month before her admission to the hospital, with cyanosis, panting respirations and vomiting. From this she recovered in three days and was well again until six days before her second admission, when abdominal pain developed, lasting a few hours and followed by rapid swelling of the abdomen and, on the next day, of the legs. There was no diarrhea or vomiting. She was found to be extremely pale, with gross edema of the lower extremities and of the abdomen up to the costal margin. There was decided tenderness over the liver area, and she was evidently in great pain, screaming during the examination. A large ascitic collection made visceral palpation difficult, but a tender, smooth liver was palpable three fingerbreadths below the costal margin; the spleen could not be felt. Distended veins coursed upward over the right costal margin. The abdominal circumference at the umbilicus was 22 inches (56 cm.). There were no other abnormal clinical findings. During the first few days following her admission, the patient's condition improved, and the liver diminished in size and tenderness. On the basis of these symptoms, a diagnosis of thrombosis of the inferior vena cava and the hepatic veins was made. Later the abdominal collateral veins became more and more obvious, extending from the lower third of the abdomen to above the costal margin, and lumbar veins also became noticeable. By two paracenteses 12 pints (5.6 liters) of pale yellow transudate were removed. After a fluctuating illness the patient eventually died, fourteen weeks after her admission to the hospital. There had never been any clinical evidence of jaundice, but, unfortunately, no biochemical evidence was sought. The serum protein content ranged from 4.2 Gm. per hundred cubic centimeters (albumin 3.12 Gm., globulin 1.08 Gm.) to 5.23 Gm. (albumin 3.32 Gm., globulin 1.91 Gm.). The lower figure was the initial one, suggesting that hepatic damage was the cause and not loss of protein into the ascitic fluid.

Abstract of Autopsy Report.—The outward appearances were similar to those described during life, namely, massive ascites with large anastomotic veins on the abdomen. The peritoneum was normal, apart from some adhesions between the liver and the diaphragm; 6 liters of ascitic fluid was present. The liver weighed 855 Gm. (normal, 390 Gm.), fixed in solution of formaldehyde. There were many dilated veins between it and the diaphragm. Its surface appeared nodular, and on section it showed necrosis of large portions, with localized areas of regeneration confined largely to the center of the right lobe. Several occluded hepatic veins could be seen, and the picture suggested hepatic necrosis secondary to venous obstruction. Histologically the liver showed marked atrophy of the greater part of the lobules, many showing only a rim of surviving cells. In a few areas there were nodules of regenerating liver. There was little fibrosis of the portal tracts. In association with a few recently thrombosed hepatic veins there was great congestion of the sinuses. The inferior vena cava was examined histologically at levels from the diaphragm to the renal veins. In the intrahepatic portion there was evidence of previous thrombosis, with organization and recanalization. The main hepatic veins entering the vena cava showed complete blockage by organized thrombus, with little recanalization. The greater portion of the vena cava at this level was patent, and the wall showed no abnormality except in relation to the organization, in which areas the muscle was thinned and in places almost completely absent; the elastica in these areas was also scanty. The part of the vena cava below the liver was narrow, with a diameter of 5.0 cm. Just above the level of the renal veins

lining membranes of the serous cavities.² It has been demonstrated further that intact erythrocytes labeled with radioactive iron³ rapidly leave the peritoneal space of the dog by way of the lymphatic vessels of the diaphragm and subsequently appear in the peripheral blood. Fortunately, in the absence of inflammation or tumor the passage of formed elements of the blood in the reverse direction is minimal and the concentration of protein in peritoneal transudates is low.⁴ Equilibrium between crystalloids of the interstitial fluids is established rapidly when various isotonic or mildly hypertonic and hypotonic fluids are injected into the abdomen.⁵ For this reason, lavage of the peritoneum has been performed in man on a few occasions in an attempt to relieve the intoxication of uremia.⁶ Although the number of reported survivals is small (two), with a practical procedure for peritoneal irrigation, such as that described by Fine and others,^{6b} and a more careful selection of cases one may anticipate better results. We desire to report treatment of a patient who died but on whom it was possible to obtain considerable data on the nitrogen and fluid balances during a period of continuous peritoneal irrigation for twenty-one days after the onset of almost complete anuria.

REPORT OF A CASE

A single white woman of 24 years of age became ill on Dec. 16, 1945, with nasopharyngitis caused by beta hemolytic streptococci. Four weeks later swelling

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centrated plasma containing 69.8 Gm. of protein. The temperature rose about 1 degree (C.) during the infusion and thereafter remained at about 38 C. (100.4 F.). The nonprotein nitrogen had now risen to 127 mg., and the carbon dioxide was 20 volumes per cent.

From this point on the greatest volume of urine obtained in a single twenty-four hour period was 132 cc. Fluids given orally were promptly vomited. Between April 8 and 10, 3,500 cc. of fluid was given parenterally, of which 500 cc. was one-sixth molar sodium *r*-lactate and 3,000 cc. was 5 per cent dextrose. Chemical examination of the blood April 10 gave these values: nonprotein nitrogen 135 mg. and creatinine 14.4 mg. per hundred cubic centimeters, carbon dioxide 29 volumes per cent, chlorides 95 milliequivalents and total plasma protein 5.8 Gm., calcium 8.7 mg. and inorganic phosphorus 14.9 mg. per hundred cubic centimeters.

We were uncertain as to the cause of the rather abrupt cessation of urine formation and wondered whether it denoted an acute exacerbation of subacute glomerulonephritis. Hoping that renal function might be reestablished in a few days if the patient could be carried through this critical period, we decided to

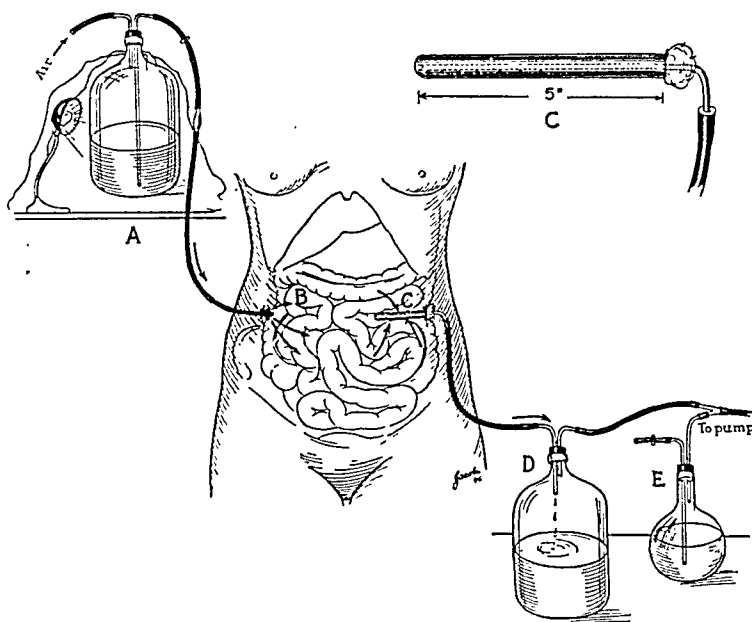


Fig. 1.—Scheme for peritoneal irrigation. *A* is reservoir of Tyrode's solution kept warm by electric light bulb. *B* is pesar catheter through which fluid was introduced by continuous drip from reservoir *A*. *C* is fenestrated brass tube entering peritoneum and serving as the "sump drain." A glass tube about half the diameter of the "sump" was passed nearly to the bottom of the brass tube and connected by rubber tubing to the collection bottle *D*. Suction was applied by a small electric pump (not shown) and the vacuum adjusted by permitting air to flow through the tube immersed in water of flask *E*.

irrigate the peritoneal cavity, following the procedure outlined by Frank, Seligman and Fine.⁷ Accordingly, the patient was removed to the operating room, and Dr. Earle Mahoney inserted a Pesar catheter into the right flank and sutured a "sump drain"⁸ to the skin, with its free end extending into the peritoneal cavity on the left

7. Frank, H. A.; Seligman, A. M., and Fine, J.: Treatment of Uremia After Acute Renal Failure by Peritoneal Irrigation, *J. A. M. A.* **130**:703 (March 16) 1946.

8. Burnett, W. E.; Rosemond, G. P., and Caswell, H. T.: The Use of the "Sump" Drain in Peritoneal Infection, *S. Clin. North America* **24**:1316, 1944.

NITROGEN AND FLUID BALANCE IN TREATMENT OF ACUTE UREMIA BY PERITONEAL LAVAGE

Analysis of Peritoneal Washings for Protein, Nonprotein Nitrogen
and Phosphorus

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A NUMBER of experiments have been conducted to test the possibilities of using the peritoneal surfaces in vivodialysis.¹ The basis for this work is the well established fact that water, crystalloids and some colloids including plasma proteins are readily absorbed by the

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1. (a) Abbott, W. E., and Shea, P.: The Treatment of Temporary Renal Insufficiency (Uremia) by Peritoneal Lavage, *Am. J. M. Sc.* **211**:312, 1946. (b) Bliss, S.; Kastler, A. O., and Nadler, S. B.: Peritoneal Lavage: Effective Elimination of Nitrogenous Wastes in the Absence of Kidney Function, *Proc. Soc. Exper. Biol. & Med.* **29**:1078, 1932. (c) Engel, D., and Kerekes, A.: Beiträge zum Permeabilitäts-problem: I. Mitteilung-Entgiftungsstudien mittels des lebenden Peritoneums als "Dialysator," *Ztschr. f.d. ges. exper. Med.* **55**:574, 1927. (d) Gantner, G.: Ueber die Beseitigung giftiger Stoffe aus dem Blute durch Dialyse, *München. med. Wchnschr.* **70**:1478, 1923. (e) Haam, E. V., and Fine, A.: Effect of Peritoneal Lavage in Acute Uremia, *Proc. Soc. Exper. Biol. & Med.* **30**:396, 1932. (f) Heusser, H., and Werder, H.: Untersuchungen über Peritonealdialyse, *Beitr. z. klin. Chir.* **141**:38, 1927. (g) Landsberg, M. and Gnoinski, H.: Recherches sur la diffusion de l'urée dans le péritoine sur le vivant, *Compt. rend. Soc. de biol.* **93**:878, 1925. (h) Rosenak, S., and Siwon, P.: Experimentelle Untersuchungen ueber die Peritoneale Ausscheidung Harnpflichtiger Substanzen aus dem Blut, *Mitt. a. d. Grenzgeb. d. Med. u. Chir.* **39**:391, 1926. (i) Seligman, A. M.; Frank, H. A., and Fine, J.: Treatment of Experimental Uremia by Means of Peritoneal Irrigation, *J. Clin. Investigation* **25**:211, 1946.

appears to be of some interest that the transudation of protein into the abdomen was greatest at the time plasma protein was being administered in large quantities. The amount of protein transfused was 623 Gm. and the amount removed 506 Gm. Vitamins were given parenterally daily, as follows: 200 mg. of ascorbic acid and 10 cc. of a soluble vitamin B preparation containing thiamine chloride, 10 mg. of riboflavin, 5 mg. of pyridoxine hydrochloride, 50 mg. of calcium pantothenate and 250 mg. of nicotinamide. Penicillin in the amount of 15,000 units was given intramuscularly every three hours, and about 100,000 units in isotonic solution of sodium chloride was used daily to apply to dressing covering the abdominal wounds. Additional penicillin was given in the irrigation fluid. Phenobarbital sodium, codeine sulfate and dihydromorphinone hydrochloride were employed as required for sedation and pain. A 10 per cent solution of "aminoids" (an oral protein concentrate in liquid form) was given by stomach tube at fairly regular intervals after the seventh day. Most of it seemed to remain in the stomach and had to be withdrawn

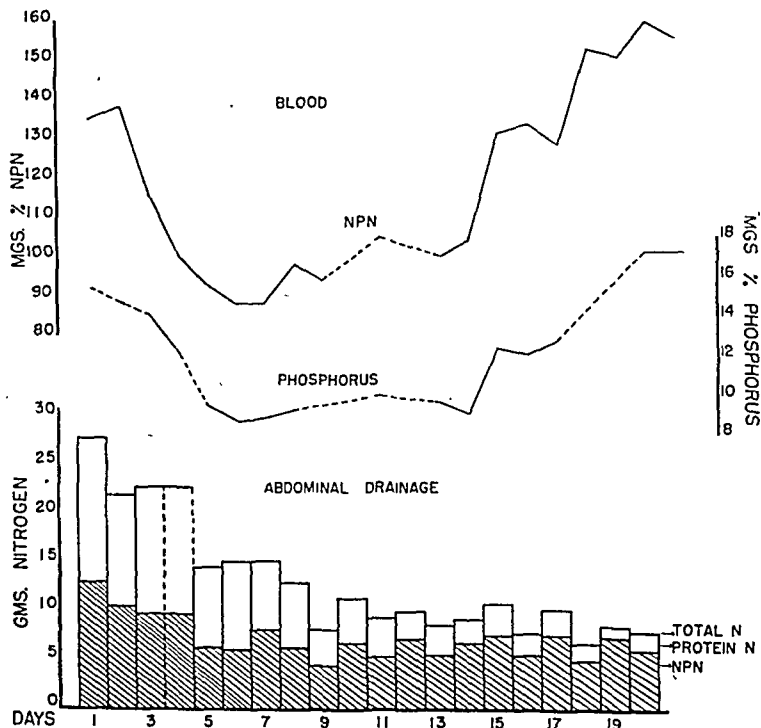


Fig. 3.—The columns represent the total amount of nitrogen removed each twenty-four hours by peritoneal irrigation. The clear portions correspond to the fraction of the total nitrogen derived from protein; the cross hatched part represents nonprotein nitrogen. Above are shown the levels of nonprotein nitrogen in whole blood and the inorganic phosphorus levels in the serum.

within the hour. The patient was relatively intolerant also of a high caloric liquid formula which was tried after infusions were discontinued.

Edema became gradually worse at first, probably because the oral intake was greater than that recorded in the table of water balance (table 1). After the tenth day the weight began to decline, and during the last few days of life the edema had largely disappeared. It was obvious that the patient had drawn heavily on her reserves of fat, but she never appeared emaciated. During the last four or five days of life she became gradually weaker. Frank pulmonary edema did not develop, but scattered rales were heard throughout both lungs. Death occurred rather suddenly on the twenty-first day after peritoneal irrigation had been initiated. The exact

of the hands was noted, the blood pressure was elevated and protein was discovered in the urine. Her general condition failed to show improvement, and she was hospitalized about ten weeks after the onset of the original illness.

Examination revealed pallor, generalized edema and elevation of the blood pressure to 165 systolic and 110 diastolic. Retinal edema, areas of arterial spasm and scattered areas of cotton wool exudate were present in the fundi. The specific gravity of the urine was 1.020, the test for protein gave a reaction of 4 plus and the sediment contained many red blood cells and hyaline casts. There was slight anemia, with a hemoglobin content of 13 Gm. per hundred cubic centimeters of whole blood and 3,800,000 red blood cells and 10,300 white blood cells per cubic millimeter. The differential count showed 88 per cent neutrophils, 8 per cent lymphocytes and 4 per cent monocytes. Study of the blood chemistry revealed a nonprotein nitrogen content of 48 mg. per hundred cubic centimeters and a serum protein level of 4.2 Gm. per hundred cubic centimeters, with an albumin-globulin ratio of 1.0. The electrophoretic patterns of the blood plasma and urinary proteins were determined later and were as follows:

	Plasma Protein, %	Urine Protein, %
Albumin*	1.02	0.69
Globulin		
	α_1 0.57	0.39
	α_2 1.30	?
	β 1.68	0.15
	ϕ 0.64	0.00
	γ 0.68	0.17
Total.....	5.89	1.40

* It will be noted that the albumin fraction was much lower when the plasma proteins were fractionated by electrophoresis. In our experience this discrepancy between the chemical and electrophoretic methods of separation of albumin from globulin occurs frequently in abnormal serums. Howe's procedure was used in the chemical separation in this case.

During the course of twenty-four hours, 1.1 Gm. of gamma globulin was excreted in the urine—about 5 per cent of the total circulating gamma globulin.

Because of maxillary sinusitis, penicillin was administered intramuscularly for fourteen days to a total dose of 2,225,000 units. Toward the end of the period it was found that the in vitro resistance of hemolytic streptococci originally cultured from the throat was high to both sulfadiazine and penicillin (60 mg. per hundred cubic centimeters for sulfadiazine and 10 units per hundred cubic centimeters for penicillin).

An attempt was made to control edema by restricting the intake of fluid and salt, but this was not successful on the general ward, and the patient was transferred to the metabolic unit on March 23. The hemoglobin content had now decreased to 10.5 Gm. per hundred cubic centimeters. Total plasma protein was 5.1 Gm. per hundred cubic centimeters.

Attempts to provide an adequate caloric and protein intake were frustrated by nausea and vomiting, and it was soon apparent that the patient's general condition was deteriorating. On April 4 it was decided to administer ammonium chloride in the hope of producing diuresis. Eight grams were given in divided doses on April 5 and 2 Gm. on April 6. The volumes of urine for April 5, 6 and 7 were 1,200, 1,400 and 1,200 cc. respectively. Administration of ammonium chloride was discontinued on April 6. Chemical examination of the blood on this date showed the nonprotein nitrogen to be 48 mg. per hundred cubic centimeters, total plasma protein 5.4 Gm. per hundred cubic centimeters, chlorides 104 milliequivalents, and cholesterol 467 mg. per hundred cubic centimeters. The last spontaneous voiding of urine was at 11 p. m. on April 7. On April 8 she was given a transfusion of 575 cc. of con-

reason for death is not known. We suspect that it was due to exhaustion and shock. Autopsy was limited to exploration of the abdominal cavity.

Observations at Autopsy (reported by Dr. Roger Terry).—The peritoneal cavity contained about 100 cc. of yellow turbid fluid, and the surface everywhere had a dull gray appearance. A fine granular layer of fibrin covered the loops of bowel. There was no evidence of a plastic exudate anywhere. The inner end of the mushroom catheter impinged on the right lobe of the liver. The "sump tube" rested in a small depression in the left psoas muscle. The omentum and several appendices epiploicae of the descending colon surrounded the inner aspect of the brass tube. Some of the fat tabs protruded through the perforations in the tube.

Stomach: There were numerous petechial hemorrhages in the mucosa in the region of the fundus. Two shallow ulcers were seen in this area.

Small Intestine: The entire wall of the small intestine appeared edematous.

Mesenteric Lymph Nodes: These were fairly large and yellowish.

Liver: Considerable fat was present in a periportal distribution in the liver. Kupffer cells in the central areas were loaded with fine yellow pigment granules.

Adrenal Glands: The left adrenal gland was of normal size and shape, and it was fairly firm. The cortex revealed a moderately thick yellowish outer zone, a thin, soft, brown inner zone and an inconspicuous gray medulla.

Kidneys: The right kidney weighed 180 Gm. and the left 215 Gm. There was a finely granular, reddish gray surface. Numerous dark red petechiae were clearly visible beneath the surface of the right kidney.

Microscopic Sections: Examination showed that all the glomeruli were altered. A few showed relatively little change except that the capillaries were bloodless or contained tiny pink thrombi, and there was some proliferation of the hyperchromatic epithelium. At the other extreme the glomeruli were almost completely replaced by fibrous tissue, with obliteration of the capillary tuft and proliferation of the basilar membrane. The tubules were generally dilated and filled by casts. The tubular epithelium was compressed and pale. Several small arteries contained organized thrombi. There was considerable proliferation of the intima of some of the large arteries.

Anatomic Diagnosis.—The anatomic diagnosis was as follows: subacute glomerulonephritis; acute generalized fibrinous peritonitis; ulcerations and erosions of the gastric mucosa; fatty liver; edema and congestion of the gastrointestinal tract; edema of the retroperitoneal connective tissue and the mucosa of the urinary bladder, and mild dependent edema.

PREPARATION OF SOLUTIONS AND ANALYTIC METHODS

Tyrode's mammalian solution was prepared every twenty-four or forty-eight hours in quantities of 18 to 20 liters. The formula and additions are given in the accompanying tabulation. All the salts except bicarbonate were dissolved in somewhat less than the required volume of sterile distilled water. The sodium bicarbonate was dissolved separately and added slowly with stirring. No precipitation occurred so long as the solution remained cool. The salt mixture was now distributed in 4 liter Erlenmeyer flasks and autoclaved. A precipitate, probably magnesium and calcium carbonate, formed but was readily brought into solution again after the flasks had cooled by passing filtered carbon dioxide through each for a few minutes, using a sterile tube and other-

(fig. 1). It was thus possible to introduce Tyrode's solution by continuous drip into the right side of the abdomen and withdraw it by gentle suction from the left side. Wangenstein suction was likewise applied through a tube introduced into the stomach. This prevented vomiting and helped to combat distention.

The composition of the perfusing fluid was kept constant except for the dextrose, which was altered depending on the degree of hydration or dehydration of the patient.^{1a} When the concentration of dextrose was low (0.1 per cent) there was a tendency for fluid to be retained, while with concentrations of 1 to 2 per cent the amount of solution withdrawn usually exceeded the quantity entering the abdomen. For the first two weeks of the procedure it was possible to keep a fairly good record of the daily exchanges of fluid, but after this leakage occurred about the inlet catheter and unknown amounts of solution were lost on the dressings and into the bed.

Clinical Course (fig. 2).—The low grade fever, which had its inception two days before lavage was started, continued until death. Tachycardia, recurring pericardial

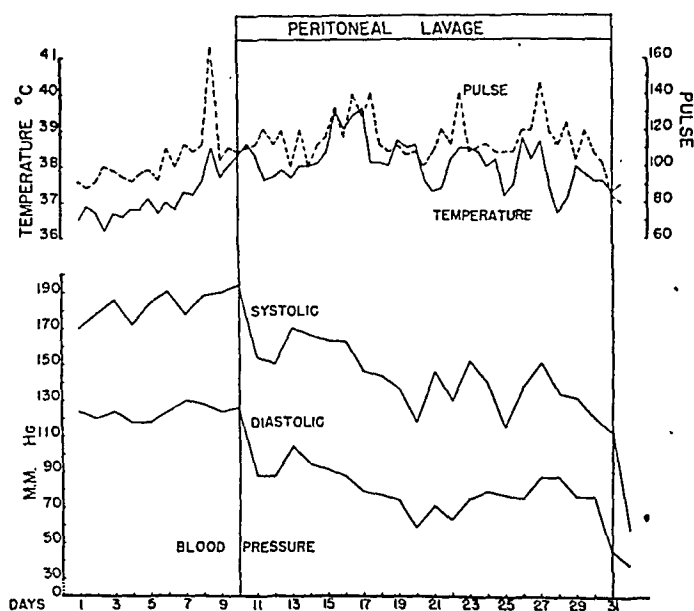


Fig. 2.—Chart of temperature, pulse and blood pressure.

friction rub, leukocytosis as high as 33,000 per cubic millimeter and intermittent delirium were also noted. The blood pressure was 194 systolic and 124 diastolic at the onset of anuria. Seven days after abdominal perfusion was begun, it had fallen to 140 systolic and 80 diastolic. It was at this time that the patient appeared distinctly improved. The duration of improvement coincided well with the fall in the levels of nonprotein nitrogen and phosphorus (fig. 3). Hypertension did not recur with increasing azotemia.

Until most of the superficial veins became thrombosed, much of the intake was intravenous. The patient was allowed to drink water freely, but a considerable part of it was returned through the Wangenstein suction. The amount of plasma protein given by vein, exclusive of plasma of whole blood, was 623 Gm. (April 11 to 17), and administration was then discontinued. Whole blood transfused between April 11 and 23 amounted to 2,000 cc. Additional fluid in the form of one-sixth molar sodium γ -lactate totaled 6,300 cc. given during the first twelve days. It

analysis of the fluid drained from the abdomen by suction as well as the behavior of the whole blood nonprotein nitrogen and serum inorganic phosphorus. During the first seven or eight days, about half of the total nitrogen in the fluid obtained by abdominal drainage was from protein and about 80 per cent of the nonprotein nitrogen was urea plus ammonia. We believe that the protein was mainly plasma protein which diffused into the peritoneal cavity. The drainage fluid was clear or slightly opalescent, and except on two occasions, to be mentioned later, it was sterile on culture. Appreciable reductions in the level of blood nonprotein nitrogen and serum inorganic phosphorus were obtained. The lowest point occurred about the sixth day, and the reductions were maintained until about the fifteenth day, when the condition of the patient became worse. From the eighth day on, less protein was removed; the concentration of nonprotein nitrogen, however, remained about the same in the drainage fluid. The decrease in diffusion of protein into the

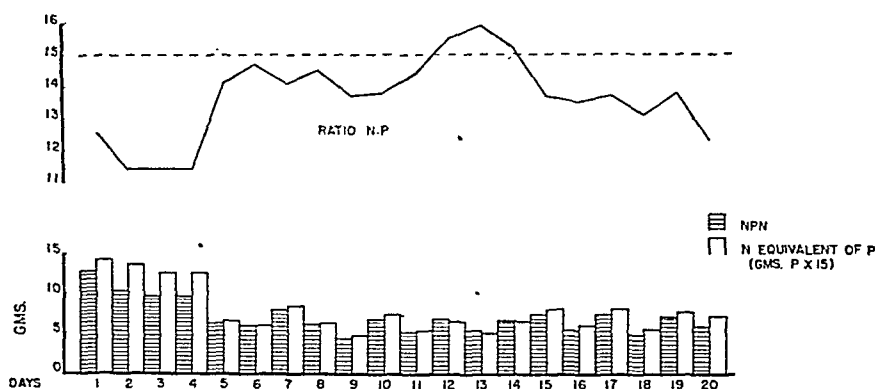


Fig. 4.—Nonprotein nitrogen and inorganic phosphorus levels of the peritoneal washings. Scale marked "Gms." refers to grams of nonprotein nitrogen in each day's collected peritoneal washings. The hatched columns represent nonprotein nitrogen of the drainage fluid, the clear columns inorganic phosphorus. The phosphorus has been plotted to a scale in which 1 Gm. of phosphorus equals 15 Gm. of nitrogen. The absolute ratio N:P is plotted as a line graph above.

abdominal cavity was not associated with any obvious lowering in the concentration of plasma protein (fig. 5), although it did coincide roughly with discontinuance of transfusions of plasma.

The amount of phosphorus removed was considerably greater than that entering with the perfusion fluid (fig. 4 and table 2). When corrections were made for the small quantity of phosphorus contained in the Tyrode solution, the ratio of nonprotein nitrogen to phosphorus was about what would be expected if protoplasm were being catabolized.¹³ Although no analyses were made, it seems improbable that calcium was

13. Reifenshtein, E. C., Jr.; Albright, F., and Wells, S. L.: The Accumulation, Interpretation and Presentation of Data Pertaining to Metabolic Balances, Notably Those of Calcium, Phosphorus, and Nitrogen, *J. Clin. Endocrinol.* 5:367, 1945. Reid, Penfold and Jones.^{6c}

TABLE 1.—*Fluid Balance**

Date, 1946	Hours	Fluid Intake			Urine	Fluid Output			Body Weight, Kg.
		Oral, Cc.	Intravenous, Cc.	Peritoneal, Cc.		Peritoneal Drainage, Cc.	Wangensteen Drainage, Cc.	Skin and Lungs, Cc.	
4/6.....	69.86
4/10 to 4/11.....	24	970+	1,500	13,120	13,060	1,100	1,000
4/11 to 4/12.....	24	2,100+	2,000	12,580	132	13,140	2,300	1,000
4/12 to 4/15.....	62½	3,560+	4,850	22,880	79	28,060	2,890	2,600
4/15 to 4/16.....	24	2,525+	525	5,600	58	7,760	2,970	1,000
4/16 to 4/17.....	24	1,350+	1,700	5,880	60	7,950	1,035	1,000
4/17 to 4/18.....	24	1,515+	2,520	12,200	26	13,560	2,380	1,000
4/18 to 4/19.....	24	1,595+	2,820	7,660	32	8,570	2,350	1,000
4/19 to 4/20.....	24	1,850+	2,500	12,250	28	4,570	2,700	1,000
4/20 to 4/21.....	24	2,450+	1,800	15,570	19	7,580	2,380	1,000	73.5
4/21 to 4/22.....	24	1,350+	2,500	15,570	31	5,830	1,670	1,000
4/22 to 4/23.....	24	1,550+	2,750	13,390	40	9,370	1,850	1,000
4/23 to 4/24.....	24	2,120+	13,390	58	5,880	3,900	1,000
4/24 to 4/25.....	24	1,990+	44	6,520	3,340	1,000
4/25 to 4/26.....	24	1,950	Leak	48	9,480	1,900	1,000
4/26 to 4/27.....	24	1,950	Leak	53	5,580	1,520	1,000
4/27 to 4/28.....	24	2,580	Leak	39	8,560	3,200	1,000
4/28 to 4/29.....	24	2,500	Leak	32	4,340	5,400	1,000
4/29 to 4/30.....	24	1,065	Leak	14	7,770	3,490	1,000	58.9
4/30 to 5/1.....	24	2,490	2,100	Leak	9	4,780	4,530	1,000

* The fluid balance as given in this table is approximate. The oral intake is known to have been somewhat above the recorded value because of inaccurate measurement of drinking water. Leaking about the intake catheter occurred to some extent on April 24, and fluid thereafter escaped in unknown amounts before entering the peritoneal cavity. The values for output are reasonably correct except for losses from the skin and lungs, which have arbitrarily been assumed to be 1 liter a day.

withdrawn from the interstitial fluid, as the concentration in the Tyrode's solution exceeded that in the serum.¹⁴

Serum Chloride, Carbon Dioxide and Protein Levels (fig. 5).— Serum chlorides were easily maintained at near normal levels, apparently as the result of free exchange of ions between the blood and the Tyrode solution. The serum bicarbonate content was low at the start but rose steadily, at first as a result of administration of sodium lactate and later probably because of withdrawal of hydrochloric acid from the stomach by Wangensteen suction.

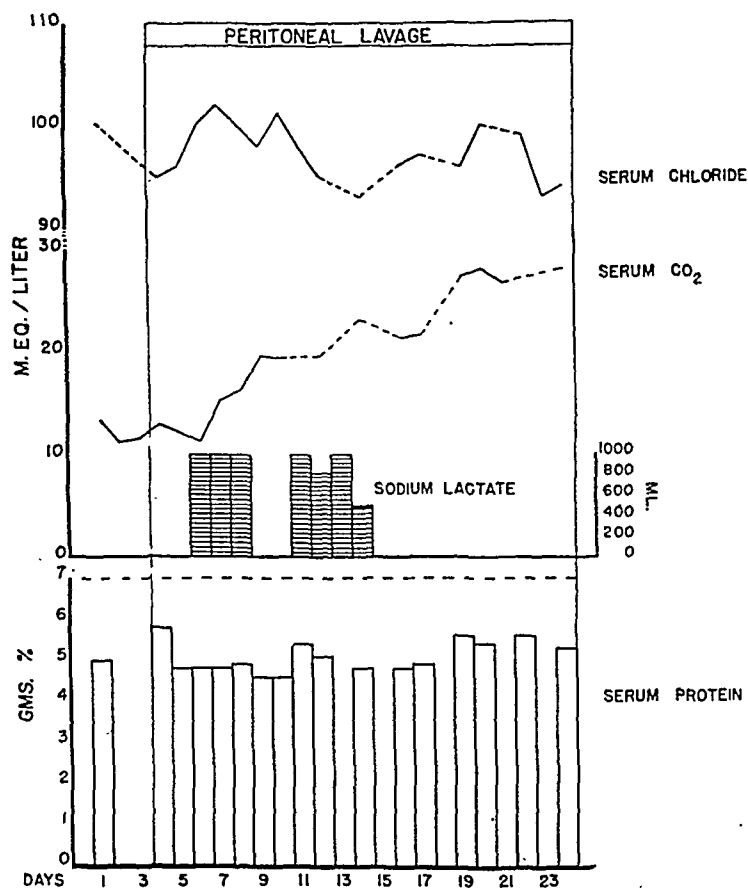


Fig. 5.—Concentration of serum chloride, carbon dioxide and protein.

A rapid fall in serum protein was anticipated when large quantities of protein were found in the drainage fluid. This did not materialize. As mentioned previously, the loss from the peritoneum was more than replaced during the first eight days by transfusions of plasma. The total loss of protein by way of the peritoneum amounted to 731 Gm. This exceeded the quantity given parenterally by about 50 Gm.

Nonprotein Nitrogen and Nitrogen Balance.—The initial fall in the concentration of nonprotein nitrogen in the blood coincided with diffu-

14. McLean, F. C., and Hastings, A. B.: Clinical Estimation and Significance of Calcium Ion Concentration in the Blood, *Am. J. M. Sc.* **189**:601, 1935.

wise observing aseptic precautions. The autoclaved solution of electrolytes was transferred to a calibrated 20 liter pyrex bottle, and sufficient freshly prepared sterile dextrose solution was added to provide the desired concentration of sugar. Any deficiency in volume was made up by the addition of sterile distilled water, and the contents were mixed by gentle shaking. Penicillin sodium, sulfadiazine sodium and heparin were introduced just prior to the connection of the bottle with the irrigation system. The modified Tyrode's solution as used for peritoneal irrigation included the following:

NaCl.....	0.9%
KCl.....	0.02%
CaCl ₂	0.02%
MgCl ₂	0.01%
NaH ₂ PO ₄	0.005%
NaHCO ₃	0.05%
Dextrose.....	0.1 to 2.5%
Additions to each 18 liters	
Sulfadiazine sodium.....	2.5 Gm.
Heparin.....	100 mg.
Penicillin sodium.....	600,000 units

The following analytic procedures were used: the serum chloride content was determined by the open Carius method,⁹ the carbon dioxide by the method of Van Slyke and Neill, the total protein by the micro-Kjeldahl method and the specific gravity by the copper sulfate method of Phillips and others.¹⁰ The total nitrogen level of the drainage fluid was estimated by the micro-Kjeldahl method, the urea plus ammonia in the drainage fluid (probably almost entirely urea) by the method of Van Slyke and Kugel¹¹ and the total nonprotein nitrogen of the drainage fluid by the micro-Kjeldahl method after precipitation of the protein with trichloroacetic acid. The protein nitrogen level of the drainage fluid was estimated as the difference between total nitrogen and nonprotein nitrogen. The nonprotein nitrogen content of the blood was determined by the method of Folin and Wu⁹ and the phosphorus content of the serum and drainage fluid by the method of Fiske and Subbarow.¹²

DATA OBTAINED

Nitrogen, Phosphorus and Protein Contents of the Drainage Fluid.—In figure 3 we have indicated the quantity of nitrogen obtained by

9. Peters, J. P., and Van Slyke, D. D.: *Quantitative Clinical Chemistry*, Baltimore, Williams & Wilkins Company, 1932, vol. 2.

10. Phillips, R. A.; Van Slyke, D. D.; Dole, V. P.; Emerson, K., Jr.; Hamilton, P. B., and Archibald, R. M.: *The Copper Sulfate Method for Measuring Specific Gravity of Whole Blood and Plasma*, *Bumed News Letter* 1:1 (June 25) 1943.

11. Van Slyke, D. D., and Kugel, V. H.: *Improvements in Manometric Micro-Kjeldahl and Blood Urea Methods*, *J. Biol. Chem.* 102:489, 1933.

12. Fiske, C. H., and Subbarow, Y.: *The Colorimetric Determination of Phosphorus*, *J. Biol. Chem.* 66:375, 1925.

elimination" effectively (table 3). The flow of nitrogen by this route was mainly into, rather than out of, the body. Had all the orally administered nitrogen absorbed during the nine day interval under discussion been retained as nonprotein nitrogen, the concentration in the blood should have increased from 105 to 217 mg. per hundred cubic centimeters.

During the last forty-eight hours, when hope for the survival of the patient had been abandoned, only non-nitrogen-containing fluids were introduced into the stomach. She drank a considerable amount of water, and fluid was withdrawn by suction at approximately hourly

TABLE 3.—*Fluid, Nitrogen and Phosphorus Recovered from the Peritoneal Cavity*

Date, 1946	Day of Lavage	Fluid Recovered, Cc.	Total Nitrogen, Gm.	Non- protein Nitrogen, Gm.	Protein Nitrogen, Gm.	Urea and Ammonia Nitrogen, Gm.	Inorganic Phos- phorus, Gm.
4/10 to 4/11.....	1	13,060	27.52	12.75	14.77	10.55	1.164
4/11 to 4/12.....	2	13,140	21.75	10.29	11.46	8.77	1.051
4/12 p. m. to 4/13 a. m.....	2½	10,000	13.44	6.23	7.21	4.45	0.589
4/13 to 4/15.....	2½ to 5	15,060	31.53	12.91	18.67	9.90	1.230
4/15 to 4/16.....	6	7,760	14.30	6.19	8.11	4.32	0.523
4/16 to 4/17.....	7	7,950	14.90	5.90	9.00	4.37	0.488
4/17 to 4/18.....	8	13,560	15.00	7.89	7.11	6.50	0.712
4/18 to 4/19.....	9	8,570	12.82	6.10	6.72	4.72	0.517
4/19 to 4/20.....	10	4,570	8.00	4.26	3.74	3.29	0.365
4/20 to 4/21.....	11	7,580	11.20	6.66	4.54	5.29	0.569
4/21 to 4/22.....	12	5,830	9.21	5.14	4.07	4.06	0.419
4/22 to 4/23.....	13	9,870	9.84	6.69	3.15	5.82	0.539
4/23 to 4/24.....	14	5,880	8.32	5.25	3.07	4.16	0.397
4/24 to 4/25.....	15	6,520	8.94	6.62	2.32	5.16	0.503
4/25 to 4/26.....	16	9,480	10.55	7.40	3.15	5.93	0.649
4/26 to 4/27.....	17	5,580	7.66	5.36	2.30	4.10	0.459
4/27 to 4/28.....	18	8,560	10.00	7.36	2.64	5.87	0.635
4/28 to 4/29.....	19	4,340	6.66	4.78	1.88	3.86	0.416
4/29 to 4/30.....	20	7,770	8.32	7.14	1.18	5.56	0.603
4/30 to 5/ 1.....	21	4,780	7.80	5.90	1.90	4.82	0.536
Totals.....			257.81	140.82	116.99	110.30	12.369

intervals. Except for some mucus, this fluid contained little protein. The nitrogen concentration was 113 mg. per hundred cubic centimeters on April 29 and 84 mg. on April 30. The corresponding chloride values were 91.3 and 76.4 milliequivalents respectively. It is evident that complete equilibrium with the extracellular water had not been obtained or the concentration of nonprotein nitrogen would have been nearly as great as that of the blood.¹⁷ Owing to the large volume of

17. Martin, L.: Total Nitrogen and Non-Protein Nitrogen Partition of Gastric Juice Obtained After Histamine Stimulation, *Bull. Johns Hopkins Hosp.* 49:286, 1931. Williams, J. L., and Dick, G. F.: The Excretion of Non-Protein Nitrogen Substances by the Intestine, *J. A. M. A.* 100:484 (Feb. 18) 1933.

TABLE 2.—*Exchange of Nitrogen and Chloride Through Gastric Intubation*

Date	"Aminoid" 10%, Cc.	"Aminoid" Nitro- gen, Gm.	"Aminoid" Chlo- ride, Gm.	For- mula, Cc.	Formula Nitro- gen, Gm.	Formula Chlo- ride, Gm.	Wangen- steen Drainage, Cc.	Wangen- steen Drainage, Nitro- gen, Gm.	Wangen- steen Drainage Chloride, Gm.	Total Nitro- gen Intake, Gm.	Total Nitro- gen Output, Gm.	Total Chlo- ride Intake, Gm.	Total Chlo- ride Output, Gm.	Wangen- steen Chlo- Drainage ride, mEq.
4/11 to 4/13*	3,440	0.98	6.08	0.98	6.08	30.2
4/13 to 4/14.....	1,170	0.41	2.07	0.41	2.07	30.2
4/14 to 4/15.....	1,680	Lost	3.33	Lost	3.33	33.8
4/15 to 4/16.....	2,970	0.76	4.38	0.76	4.38	25.2
4/16 to 4/17.....	1,685	0.64	2.42	0.64	2.42	24.5
4/17 to 4/18.....	965	6.56	2.23	2,380	6.50	6.63	6.56	6.50	2.23	6.63	48.0
4/18 to 4/19.....	1,045	7.10	2.41	2,350	7.57	7.30	7.10	7.57	2.41	7.30	53.1
4/19 to 4/20.....	1,035	7.05	2.39	2,700	6.20	9.12	7.03	6.20	2.39	9.12	57.8
4/20 to 4/21.....	1,300	8.85	3.00	2,380	7.44	10.71	8.85	7.44	3.00	10.71	77.0
4/21 to 4/22.....	900	6.12	2.08	1,070	3.32	7.63	6.12	3.32	2.08	7.63	77.6
4/22 to 4/23.....	900	6.12	2.08	1,850	2.62	9.55	6.12	2.62	2.08	9.55	88.2
4/23 to 4/24.....	800	5.44	1.85	840	9.36	2.66	3,960	8.30	24.00	14.80	8.30	4.51	24.00	103.6
4/24 to 4/25.....	600	4.08	1.38	900	10.00	2.85	3,340	8.18	22.50	14.08	8.18	4.23	22.50	115.0
4/25 to 4/26.....	900	6.12	2.08	450	5.00	1.43	1,900	5.05	11.57	11.12	5.05	3.51	11.57	104.0
4/26 to 4/27.....	500	3.40	1.15	300	3.33	0.95	1,520	2.87	9.96	6.73	2.87	2.10	9.96	112.0
4/27 to 4/28.....	1,200	8.16	2.77	400	4.45	1.27	3,200	8.40	18.55	12.01	8.40	4.04	18.55	99.2
4/28 to 4/29.....	1,100	7.48	2.54	400	4.45	1.27	5,400	15.50	34.70	11.93	15.50	3.81	34.70	109.8
4/29 to 4/30.....	3,490	3.96	18.65	3.96	18.65	91.3
4/30 to 5/1.....	4,520	3.80	20.20	3.80	20.20	76.4

* Values obtained at 3:30 p. m. on April 11 and at noon on April 13.

chance of resolution of the lesion in the kidney within two or three weeks is good. Renal decapsulation and biopsy have been tried and might be of advantage in suitable cases.¹⁰ One might even question whether the procedure increases the chance of survival beyond that of more conventional methods of treatment. While it is usually thought that the victim of complete anuria will succumb within eight or ten days, survivals for twenty to thirty days are not unknown.¹⁰ In the procedure's favor are a number of animal experiments in which the survival time of nephrectomized dogs was increased over that of controls¹⁸ and a small series of observations on rabbits that survived a lethal dose of mercuric chloride.¹⁰

The technical problems presented are those of infection, nutrition, hydration and regulation of the acid-base balance.

Infection.—Cultures of the peritoneal washings revealed the presence of *Bacillus aerogenes* on two occasions—on the third day of irrigation and again at autopsy. On the sixteenth day of irrigation diphtheroids were recovered. Other cultures were sterile. The inclusion of antibiotics in the lavage fluid and the aseptic technic seem to be reasonable assurance against serious infection of the peritoneum. The concentration of penicillin sodium in the lavage fluid was raised from 1,660 units per liter to 3,300 units when it was found that the fluid in the outflow tube failed to inhibit growth of test organisms in vitro. Satisfactory inhibition was found at the higher concentration. The presence of fibrinous peritonitis was demonstrated at autopsy, but whether this was the result of bacterial infection or of chemical irritation is not known.

Nutrition.—Because of nausea and vomiting accompanying the uremia, oral feeding did not prove feasible. Parenteral feeding was partially successful, but the caloric intake was far from adequate, so that a large part of the energy required by the patient must have been derived from consumption of her own tissues.

Plasma Protein in the Peritoneal Washings.—The removal of large amounts of plasma protein in the peritoneal washings is something that has not been mentioned previously. Putnam²⁰ found small amounts of protein in the fluid withdrawn from the peritoneal cavity after injection of isotonic solution of sodium chloride. Balazs and Rosenak^{6a} recovered protein in the amount of one-third per cent in the peritoneal washings when a 4.5 per cent solution of dextrose was introduced into the abdominal cavity in a case of mercury poisoning. Iversen and Johansen¹⁹ noted about 0.5 per cent of protein in ascitic fluid dur-

18. Abbott and Shea.^{1a} Bliss and others.^{1b} Rosenak and Siwon.^{1h} Seligman and others.¹ⁱ

19. Iversen, P., and Johansen, E. H.: Pathogenese und Resorption von Trans- und Exudation in der Pleura, *Klin. Wchnschr.* 8:309, 1929.

sion of urea and other nitrogenous bodies into the irrigation fluid. In spite of the fact that a fairly constant amount of nitrogen (nonprotein) was removed each twenty-four hours from the fifth day until death, there was a rather abrupt rise in the level in the blood about the fourteenth day. Prior to this time, edema was severe. It began to subside as the nonprotein nitrogen level rose. Unfortunately a leak along a sinus forming about the abdominal inflow catheter happened to coincide with the period of decline in weight. This permitted some of the fluid from the reservoir to escape without traversing the peritoneal cavity. The "sump" continued to function satisfactorily, but as an accurate record of the inflow could not be obtained, no record of edema fluid which may have been lost as peritoneal transudate is available. The amount of nonprotein nitrogen removed from the fluid obtained by lavage was 6.07 Gm. a day between April 15 and 20 while the edema was intense; with loss of 14.6 Kg. in weight between April 20 and 29, the average amount of nonprotein nitrogen recovered was 6.21 Gm. a day.

The following calculation demonstrates how loss of water from the body without a corresponding loss of nitrogen could account for the increased concentrations of nonprotein nitrogen in the remaining body fluids:¹⁵

April 20

Body weight	73.5 Kg.
Blood nonprotein nitrogen.....	105 mg.
Edema-free weight of body.....	58.9 Kg. (as of April 29)
Nonprotein nitrogen content of body water, $58.9 \times 0.7 \times 1.05 =$	43.3 Gm.
Nonprotein nitrogen content of edema fluid, $14.6 \times 1.05 =$	15.3 Gm.
Total.....	58.6 Gm.

April 29

Body weight (essentially edema free).....	58.9 Kg.
Blood nonprotein nitrogen.....	150 mg.
Nonprotein nitrogen content of body water, $58.9 \times 0.7 \times 1.50 =$	61.9 Gm.

Two avenues for the escape of water from the body were open, which in the circumstances did not permit simultaneous loss of the nitrogen of edema fluid. These were (a) evaporation from the skin and lungs and (b) withdrawal of excess fluid by gastric suction. We estimated that the amount withdrawn was 6 Kg. during the period of dehydration. Although it is maintained that nitrogen may be lost from the body in appreciable amounts by way of gastric and intestinal secretion in uremia,¹⁶ the introduction of an amino acid solution and protein from a formula into the stomach seems to have blocked such "vicarious

15. Peters, J. P., and Bulger, H. A.: The Relation of Albuminuria to Protein Requirement in Nephritis, *Arch. Int. Med.* **37**:153 (Feb.) 1926.

16. Meyers, W. A.: (a) Obstructive Anuria: Report of a Remarkable Case, *J. A. M. A.* **85**:10 (July 4) 1925; (b) Long Standing Anuria: Certain Associated Phenomena, *ibid.* **86**:1198 (April 17) 1926.

transudate from the interstitial fluid all the protein removed could be accounted for. The opportunity for the establishment of equilibrium is favorable. The area of the peritoneal surfaces is large—about equal to that of the surface area of the body.²¹ The rate of infusion of fluid did not exceed 9 cc. per minute and was usually considerably less than this. Fluid was continually withdrawn, and it is unlikely that any considerable pooling occurred. The autopsy revealed no adhesions or evidence of channeling. The fall in the concentration of protein in the washings after about eight to ten days was definite. While at autopsy there was no evidence of acute infection, it was obvious that there had been some irritation of the membranes since they were covered with a thin layer of fibrin. Possibly this coating of fibrin decreased the permeability to protein in the later stages of perfusion. Urea and inorganic phosphorus were found in the outflow in about as high a concentration as previously, which would indicate little change in permeability with regard to crystalloids. Another possibility is that the nephritic process was more acute at the start and that since acute nephritis is supposed to be associated with generally increased capillary permeability²² more protein passed through the capillary wall. Against this supposition are the observations of Warren and Stead,^{20a} who found the concentration of protein in interstitial fluid in acute nephritis no higher than in other edematous states. Nevertheless, the possibility that capillary permeability may have been greater in the early stage of the lavage process remains intriguing. To quote from Peters and others,^{22c} “there can be little doubt, in view of the retinal lesions, the hypertension and other circulatory changes, that the pathological manifestations of acute nephritis are not confined to the kidney but involve the general vasculature of the body.”

Hydration.—Difficulty in moving the patient interfered with frequent weighing. An approximate fluid balance is given in table 1. As it was impossible to measure the loss through the skin and lungs, a value for this was arbitrarily assigned of 1,000 cc. each day. In many instances the records of the oral intake were not accurately kept because of allowing the patient to hold cracked ice in her mouth, and no doubt the quantity often exceeded that given in the table. On April 19, the

21. Hertzler, A. E.: *The Peritoneum*, St. Louis, C. V. Mosby Company, 1919, vol. 1, p. 113. Wegner, G.: *Chirurgische Bemerkungen über die Peritonealhöhle mit besonderer Berücksichtigung der Ovariectomie*, Arch. f. klin. Chir. **20**:64, 1877.

22. (a) Beckmann, K.: *Odemstudien*, Deutsches Arch. f. klin. Med. **135**:39, 1921. (b) Fishberg, A. M.: *Hypertension and Nephritis*, ed. 4, Philadelphia, Lea & Febiger, 1939. (c) Peters, J. P.; Bruckman, F. S.; Eisenman, A. J.; Hald, P., and Wakeman, A. M.: *The Plasma Proteins in Relation to Blood Hydration*: VII. A Note on the Proteins in Acute Nephritis, J. Clin. Investigation **2**:97, 1932. (d) Van Slyke and Kugel.¹¹

fluid withdrawn, 7.7 Gm. of nitrogen was removed on these two days. The nitrogen balance was as follows:

Nitrogen intake		
Whole blood.....	63.3 Gm.	
Plasma.....	99.6 Gm.	
"Aminoids".....	76.5 Gm.	
Special formula.....	36.6 Gm.	
	<hr/>	
	276.0 Gm.	276.0 Gm.
Nitrogen output		
Peritoneal drainage		
(a) Nonprotein nitrogen.....	140.8 Gm.	
(b) Protein nitrogen.....	117.0 Gm.	
Gastric suction.....	92.5 Gm.	
Urine.....	4.4 Gm.	
	<hr/>	
	354.7 Gm.	354.7 Gm.
	<hr/>	
Difference (nitrogen loss).....		78.7 Gm.

The over-all nitrogen balance revealed a loss to the patient of 80 to 90 Gm. of nitrogen. The values given for the intake are reasonably complete, while the output is somewhat less than it should have been because, of three stools passed, all were lost in the bed. Another avenue of elimination of nitrogen which may be important in uremia is the skin. Measurement of excretion of nitrogen by this route is difficult under the most favorable conditions and in the present circumstances was found impracticable.

It will be noted that 72.0 per cent of the total output was from the peritoneal cavity and that almost half of this amount was protein. Returns of gastric suction accounted for 26.2 per cent, of which the major part seems to have been nitrogen from unabsorbed food. Only 1.2 per cent of the nitrogen output was found in the urine. On the intake side, whole blood and plasma accounted for 59 per cent and actually represent the main source of nitrogen available to the patient. The exchanges of protein nitrogen almost balanced each other; 153 Gm. was added to the body pool by transfusion of whole blood and plasma, and 141 Gm. was removed by peritoneal lavage. Thirty-one grams of food nitrogen seems to have been absorbed, or 11.2 per cent of the intake from all sources.

COMMENT

The choice of peritoneal lavage as a therapeutic procedure presents several technical problems as well as moral issues. It is obviously unjustified if there are sound reasons for the belief that renal function can never be reestablished at a level compatible with survival. In our experience, at least, it adds greatly to the discomfort of the patient and to the mental anguish of the family and friends. We believe that it should not be attempted unless the onset of the anuria is acute and the

TABLE 4.—Blood Chemistry

Date, 1946	Day of Lavage	Non-protein Nitrogen, Mg. %	Blood Urea Nitrogen, Mg. %	Creatinine, Mg. %	Uric Acid, Mg. %	Chloride, mEq.	Carbon Dioxide, Vol. %	Serum Protein, Gm. %*	Inorganic Phosphorus, Mg. %	Calcium, Mg. %	Sugar, Mg. %	Cholesterol, Mg. %	Sulfadiazine, Mg. %
4/6.....	..	48	104	30	5.0 G	8.5	...	467	...
4/8.....	..	114	25
4/9.....	..	127	26
4/10.....	..	135	..	14.4	...	95	20	5.8 G	14.9	8.7
4/11.....	1	138	..	12.6	...	96	27	4.8 G
4/12.....	2	115	84	11.3	...	100	25	4.8 G	14.0	...	184
4/13.....	3	100	..	10.6	...	102	34	4.8 G	12.1
4/14.....	4	93	70	10.5	6.2	100	36	5.0 G	9.4	8.2
4/15.....	5	88	66	9.6	7.6	98	43.5	4.6 K	8.6	8.6	...	144	...
4/16.....	6	88	66	10.9	...	101	43	4.6 K	8.7	...	130
4/17.....	7	98	71	10.4	9.2	98	..	5.4 G	9.2	...	106
4/18.....	8	94	..	10.3	...	95	43.5	5.1 G	2.6
4/20.....	10	105	79	10.8	9.0	93	51	4.8 G	9.9	...	95	222	2.3
4/22.....	12	100	84	10.8	7.1	96	47.5	4.8 G	9.6	7.0	77	...	2.4
4/23.....	13	104	97	48	4.9 G	9.1	...	53
4/25.....	15	131	97	11.1	8.7	96	60.5	5.6 G	12.3	...	84
4/26.....	16	133	101	10.7	8.6	100	62	5.4 G	12.0	5.0
4/27.....	17	128	118	10.6	8.9	...	57	12.7	...	110
4/28.....	18	152	124	10.9	9.5	99	..	5.6 G	100
4/29.....	19	150	136	93
4/30.....	20	159	106	11.1	10.4	94	60	5.3 G	17.2	...	110	243	...
5/1.....	21	155	106	10.9	12.1	100	62	5.4 G	17.2	7.6	92

* G indicates the value when calculated from the specific gravity of the serum and K the value when calculated as total serum nitrogen minus nonprotein nitrogen multiplied by 6.25.

ing the initial stages of transudation. In the experiments of Schechter and others^{2d} on normal dogs, protein appeared to diffuse slowly into isotonic solution of sodium chloride introduced into the peritoneum. They felt that whatever fluid was introduced into the peritoneal cavity tended to assume the composition of the interstitial fluid, which almost certainly contains small quantities of protein.²⁰ The actual concentration of protein in the peritoneal washings was small and varied from about 0.7 per cent during the first days of lavage to from 0.2 to 0.25 per

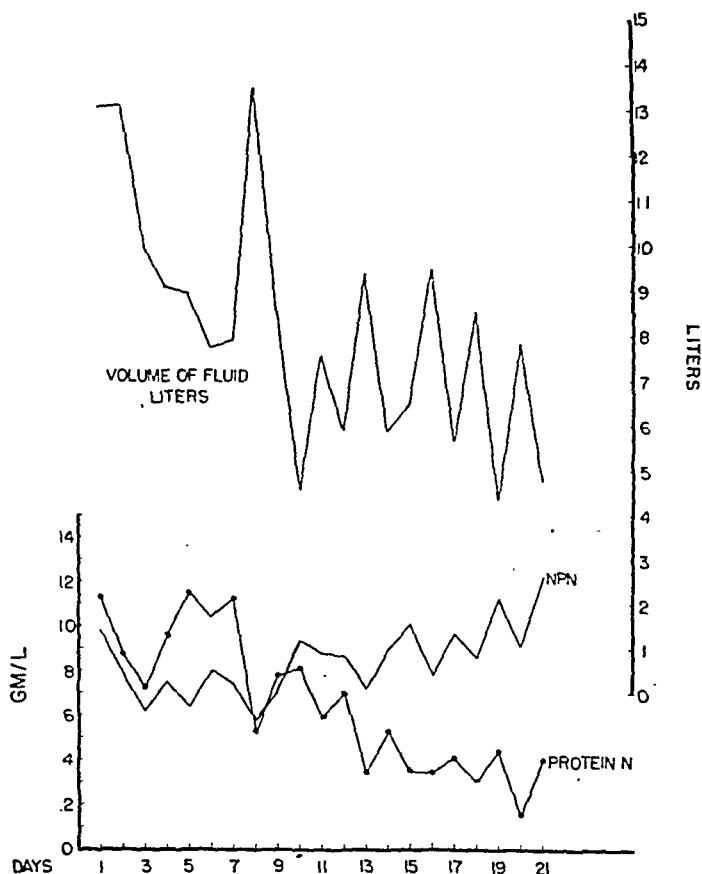


Fig. 6.—Concentration of protein nitrogen and nonprotein nitrogen as related to volume of peritoneal drainage. The concentration of protein nitrogen decreased progressively during the period of lavage, while that of nonprotein nitrogen tended to increase. An inverse relation between the volume of drainage and the concentration of nonprotein nitrogen is evident.

cent after about twelve days (fig. 6). In view of the large amount of fluid withdrawn, even this small concentration of protein resulted in a significant loss. Thus it would appear that should there be time for the fluid which is introduced to assume the characteristics of a simple

20. (a) Warren, J. V., and Stead, E. A., Jr.: The Protein Content of Edema Fluid in Patients with Acute Glomerulonephritis, *Am. J. M. Sc.* **208**:618, 1944.
 (b) Peters.⁴

EXCRETION OF NICOTINIC ACID IN TYPHOID

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THE LITERATURE contains many reports on the association of typhoid and pellagra. Bean and others,¹ in a review on secondary pellagra, assumed that in typhoid the rise in metabolism due to the prolonged fever leads to increased demands on the system of catalysts and brings about a state of deficiency. Sarma² in 1943 described the deficiency of nicotinic acid in patients with typhoid. Symptoms of this condition were glossitis and cerebral disturbances such as mania, confusion, delirium and melancholia. These symptoms could be relieved by treatment with nicotinic acid. Deficiency of nicotinic acid following typhoid has been observed in the Hadassah Rothschild University Hospital as well.³ However, no laboratory investigations on the metabolism of nicotinic acid in typhoid have as yet been reported.

The study reported here was undertaken with the purpose of examining the urinary excretion of nicotinic acid in typhoid and of establishing a possible relationship between the rate of excretion of the acid and the clinical symptoms of its deficiency.

MATERIALS AND METHODS

Excretion of nicotinic acid⁴ in the urine was studied in 17 cases of typhoid, in 4 of which the level of nicotinic acid in the blood was determined as well. The duration of the febrile period in these cases ranged from ten to forty-two days, with an average of twenty-five days. The first examination of the urine was performed after typhoid had been diagnosed, and frequent examinations were subsequently made during the febrile and convalescent periods.

Dr. Braun is from the Department of Medicine, Division B, Hadassah Rothschild University Hospital, and Dr. Grossowicz is from the Department of Hygiene and Bacteriology, The Hebrew University.

1. Bean, W. B.; Spies, T. D., and Blankenhorn, M. A.: Secondary Pellagra. *Medicine* **23**:1 (Feb.) 1944.

2. Sarma, A. V. S.: Use of Nicotinic Acid in Treatment of Typhoid Fever, *J. Indian M. A.* **13**:74 (Dec.) 1943.

3. Braun, K., and Kornblueth, W.: Secondary Deficiency Diseases, *Acta med. orient.* **2**:37 (March) 1943.

4. In this paper the term nicotinic acid is used to denote the combination of nicotinic acid and nicotinamide.

ninth day of peritoneal irrigation, the weight was 73.5 Kg., a gain of 3.7 Kg. from the last previous weighing on April 6. There was considerable pitting edema of the extremities and back. In order to determine whether as much fluid was being removed as was introduced into the peritoneal cavity, careful records were kept of the rate of inflow and outflow on several occasions when Tyrode's solution contained between 1 and 2 per cent dextrose:

Date	Hours	Inflow	Outflow	Difference
April 14.....	12	4,180 cc.	4,820 cc.	640 cc.
April 16.....	10½	1,840 cc.	2,600 cc.	760 cc.
April 18 to 19.....	24	7,660 cc.	8,570 cc.	910 cc.

In each instance considerably more fluid was removed than was put in. This agreed with the observations of Abbott and Shea²² in dogs. Increasing the concentration of dextrose in the Tyrode solution seems to be an effective means of preventing excessive absorption of fluid from the peritoneum.

Acid-Base Balance.—The acid-base balance is shown in figure 5 and table 4. The usual fall in bicarbonate content of the plasma had occurred at the onset of uremia. The Tyrode solution which we employed contained only 0.05 per cent of sodium bicarbonate, or approximately 6 millimols per liter. Establishment of an equilibrium between the interstitial fluid and the Tyrode solution should have increased the acidosis, since it is improbable that bicarbonate would have been selectively absorbed by the peritoneum.³ The increasing concentration of bicarbonate in the serum must have been dependent on (a) administration of one-sixth molar sodium *r*-lactate solution intravenously and (b) removal of chloride ion from the stomach. With the application of Hartmann's formula,²³ the amount of one-sixth molar sodium *r*-lactate required to raise the plasma carbon dioxide from its initial level of 25 to 60 volumes per cent was 4,400 cc. Essentially this result was accomplished over a period of nine days by infusion of 6,300 cc. No lactate was administered during the last ten days of life, yet the plasma carbon dioxide gradually increased from 50 to 60 volumes per cent. The chloride content of the fluid aspirated from the stomach increased greatly at this time and, since it was highly acid, must have contained a considerable excess of chloride ion, thus freeing sodium to combine with bicarbonate. Since the concentration of other anions measured in the serum did not diminish in proportion to the increase in bicarbonate, an increase in total base is to be suspected. Positive evidence on this point was not obtained for lack of sodium or total base determinations. It would have been important also to have had obser-

23. Hartmann, A. F., and Senn, M. J. E.: Studies in Metabolism of Sodium *r*-Lactate: II. Response of Human Subjects with Acidosis to the Intravenous Injection of Sodium *r*-Lactate, *J. Clin. Investigation* **11**:337, 1932.

determinations of nicotinic acid in the urine (Goldsmith, 1.2 mg. per liter,¹⁰ and Perlzweig and others, 1.0 to 3.0 mg. per liter¹¹).

Sixteen of the 17 patients with typhoid showed a gradual decrease in the amount of excretion of nicotinic acid during the course of the infection. The amount excreted at the onset of the disease was normal or sometimes above the normal, the average being 2.55 mg. per liter. As the disease progressed, a steady decrease in excretion was noted, the minimal excretion being observed in the course of the convalescent period (fig. 1), during which time the average value was 0.59 mg. per liter. Excretion curves typical of the various stages of the disease are presented in figures 2 and 3. Both curves show that the initial excretion of nicotinic acid was above normal. The lowest values occur late

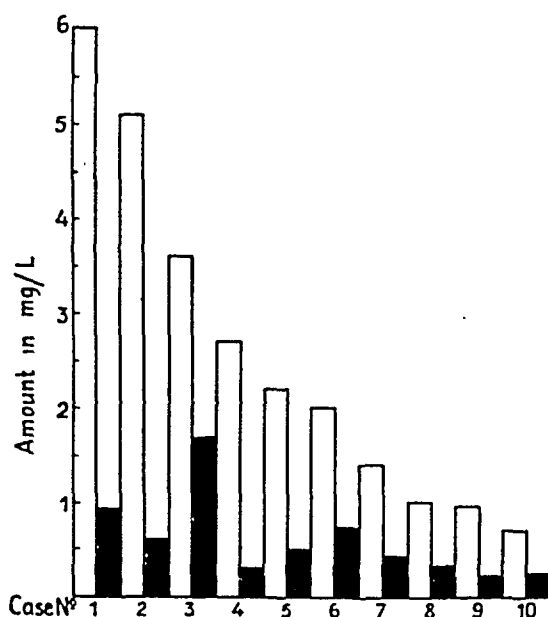


Fig. 1.—Excretion of nicotinic acid (niacin) in 10 cases of typhoid. The white columns indicate initial values and the black columns terminal values.

in the convalescent period (in figure 2 eight days and in figure 3 as late as twelve days after the fever had subsided). The effect of treatment with nicotinic acid on excretion is demonstrated in figure 2. Administration of 600 mg. daily for five days was followed by a rise in the excretion from 0.6 mg. to 5.5 mg. per liter. In only 1 of the 17 cases studied was there any considerable change in excretion. The patient in this case had mild typhoid and was admitted to the hospital three days after the onset of pyrexia. Excretion of nicotinic acid on the pa-

10. Goldsmith, G. A.: Urinary Excretion of Nicotinic Acid and Its Derivatives, *Arch. Int. Med.* **73**:410 (May) 1944.

11. Perlzweig, W. A.; Levy, E. D., and Sarett, H. P.: Nicotinic Acid Derivatives in Human Urine and Their Determination, *J. Biol. Chem.* **136**:729 (Dec.) 1940.

variations on the level of serum potassium. Only one specimen of serum was analyzed for potassium, on the sixteenth day of irrigation, when the level was 5.9 milliequivalents.

SUMMARY

Peritoneal irrigation was carried on continuously for twenty-one days in a patient with subacute glomerulonephritis who became almost completely anuric two days before the irrigation was started. Flow of urine was not reestablished, and the patient died. The total nitrogen removed by way of the peritoneal cavity was 257.8 Gm. Of this amount, 140.8 Gm. was nonprotein nitrogen and 117 Gm. protein nitrogen. The former was fractionated into urea and ammonia nitrogen 110.3 Gm. and undetermined nitrogen 30.5 Gm. Substantial reductions in the concentration of blood nonprotein nitrogen and serum inorganic phosphorus were obtained at first, but as the patient lost edema fluid, these values rose above the pretreatment levels. This is thought to have been due to a more rapid loss of water from the body than of nonprotein nitrogen, rather than to an increase in nitrogen catabolism.

Bicarbonate in the plasma increased from 25 to 60 volumes per cent because of the administration of sodium lactate solution intravenously and the withdrawal of chloride in excess of base from the stomach.

Dr. Eric L. Alling prepared the electrophoresis of plasma and urine protein and Dr. Roger Terry the pathologic report.

Note.—Since completion of the manuscript of this paper, another report on the treatment of acute anuria due to sulfadiazine has appeared.²⁴

24. Doenges, J. P., and Strahan, C.: Treatment of Acute Sulfadiazine Anuria by Continuous Peritoneal Lavage, *Bull. School Med., Univ. Maryland* **31**:89, 1947.

Of the 16 patients with decreased excretion of nicotinic acid, 5 had glossitis as the only objective sign characteristic of deficiency. No specific clinical symptoms were observed in the other 11 patients except that they complained of general weakness, muscular pain and difficulty in concentration. These symptoms may have been due to latent vitamin deficiency, but they are indistinguishable clinically from similar symptoms attributable to the toxemia of typhoid.

COMMENT

The results reported show that there is a progressive drop in urinary excretion of nicotinic acid during the course of an attack of typhoid. The diet given to our patients contained 9.1 mg. of nicotinic acid daily, an amount sufficient to prevent deficiency.⁷ Thus it seems that the diet is not responsible for the decrease in the excretion of nicotinic acid, which must therefore be attributed to intrinsic factors connected with the disease. Factors which may be implicated are: (1) diarrhea, causing loss of vitamins; (2) an inflammatory state of the intestines, interfering with the absorption and utilization of nutrients; (3) interference with the intestinal synthesis of nicotinic acid, and (4) increased vitamin requirements due to the prolonged fever.

The first possibility can be eliminated, since none of our patients had diarrhea. The second possibility cannot easily be ruled out, as the pathologic changes may be severe and may involve a large part of the small intestines and its lymphatic vessels. However, the fact that excretion of nicotinic acid was at its lowest late in the period of convalescence, when the repair of the lesions had already taken place, argues against this contention. It may be added that our patients responded to the administration of nicotinic acid with a considerable rise in excretion of the acid, indicating that absorption was not seriously impaired. Interference with intestinal synthesis of nicotinic acid is a possibility, since a disturbance in the equilibrium between the various bacteria normally present in the intestines may have occurred, leading to a decrease in the amount of nicotinic acid available.¹³ The factor most likely to be responsible for the observed variations in excretion of nicotinic acid is typhoid itself, with its accompanying metabolic changes. The prolonged course of fever in typhoid is associated with an increased catabolism of foodstuffs and essential metabolites. Shaffer and Coleman¹⁴ found a greatly increased rate of urinary excretion of nitrogen in typhoid, leading to a negative nitrogen balance. If

13. Benesch, R.: Synthesis and Destruction of Nicotinic Acid by Mixed Caecal Flora of Man, *Lancet* 1:718 (June 9) 1945.

14. Shaffer, R. A., and Coleman, W.: Protein Metabolism in Typhoid Fever, *Arch. Int. Med.* 4:538 (Dec.) 1909.

Urine was collected for twenty-four hours and pooled in a solution of acetic acid in a final approximately tenth-normal concentration. Samples of the specimens of urine were diluted twenty times with distilled water, sterilized and stored in a refrigerator till the day of examination. The amount of nicotinic acid plus nicotinamide was determined by a modification of the microbiologic method described by Lwoff and Querido (Grossowicz and Sherstinsky⁵). The growth rate of *Proteus* X 19 was used for the quantitative determination of both nicotinic acid and nicotinamide. One-tenth to 2 cc. of the diluted urine is needed for this improved test, in which the sensitivity lies between 0.01 and 0.1 micrograms per 10 cc. of the medium.

The blood was diluted 1:20 with distilled water, and the proteins were removed by the method of Isbell and others.⁶ The nicotinic acid content of the blood was determined by the method just described, 0.5 cc. of blood being required for each examination.

Composition of the Test Diet.—During the entire febrile period our patients received the high nutritional, low residual diet customary in cases of typhoid—5 eggs, 1 liter of milk, 300 cc. of bouillon, 400 cc. of milk custard and 200 Gm. of fruit juice. Meat was added to this diet after the fever had subsided. The daily intake of fluid was approximately 3 liters.

The nicotinic acid content of this diet was determined as follows: The total daily intake of food was collected from the kitchen, homogenized and suspended in distilled water. The average daily intake of nicotinic acid was found to be 9.1 mg. This amount, though less than the allowances recommended by the United States National Research Council, which average about 15 mg. for normal adults, is sufficient to prevent pellagra or any other sign of deficiency.⁷ Dann,⁸ in summarizing dietary investigations among various classes of the American population, concluded that the minimal daily requirement of nicotinic acid for a man weighing 70 Kg. is less than 10 mg.

RESULTS

The normal values obtained by our method in healthy controls ranged from 1.0 to 2.5 mg. per liter per day. Johnson and others,⁹ using a different microbiologic method, recorded 1.8 to 4.0 mg. per liter as normal values. Similar results have been obtained with chemical

5. Grossowicz, N., and Sherstinsky, E.: An Improved Microbiological Method for the Determination of Nicotinic Acid Based on the Use of *Proteus* HX19, *J. Biol. Chem.*, to be published.

6. Isbell, H.; Wooley, J. G.; Butler, R. E., and Sebrell, W. H.: A Bacterial Assay Method for Nicotinamide and Related Substances in Blood, Urine and Spinal Fluid, *J. Biol. Chem.* **139**:499 (June) 1941.

7. Winters, J. C., and Leslie, R. E.: A Study of the Diet and Nutritional Status of Women in a Low Income Population Group, *J. Nutrition* **26**:443 (Nov.) 1943.

8. Dann, W. J.: The Human Requirement for Nicotinic Acid, *Federation Proc.* **3**:159 (Sept.) 1944.

9. Johnson, B. C.; Hamilton, T. S., and Mitchell, H. H.: The Excretion of Nicotinic Acid, Nicotinamide, Nicotinuric Acid and N-Methylnicotinamide by Normal Individuals, *J. Biol. Chem.* **159**:231 (June) 1945.

SUMMARY

Excretion of nicotinic acid in the urine was studied in 17 cases of typhoid. In 16 of these there was a gradual and progressive drop from an average maximum value of 2.55 mg. per liter at the onset to 0.59 mg. per liter during convalescence.

In only 5 of these cases did glossitis develop during convalescence, while in the other 11 there were no specific clinical signs of deficiency of nicotinic acid.

Intensive dietary treatment, with the addition of vitamins to the diet, is suggested as a preventive against vitamin deficiency.

The question of a specific relationship between typhoid and diminished excretion of nicotinic acid is discussed.

NOTE.—Since this paper was submitted for publication 8 more cases of typhoid have been examined, and values for excretion of nicotinic acid in the course of the disease were found to be similar to those reported here. Identical results were obtained from the calculation of the excretion in milligrams per liter and the calculation of the total daily urinary output of nicotinic acid in the entire 24 cases investigated.

tient's admission was already extremely low (0.55 mg. per liter). The fever lasted for ten days only, and during convalescence the excretion fell to 0.5 mg. per liter.

In 4 patients whose blood was examined no pronounced variation in the amount of nicotinic acid were found. This is in accord with

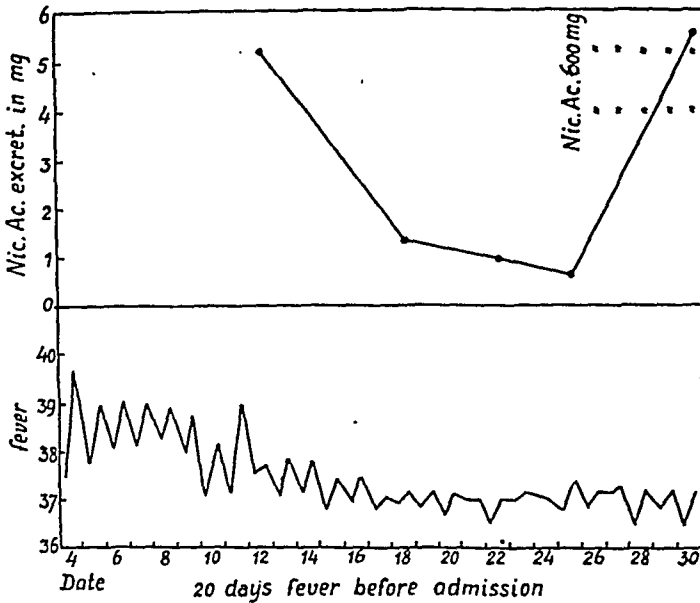


Fig. 2.—Excretion of nicotinic acid in the course of typhoid and effect of treatment on excretion.

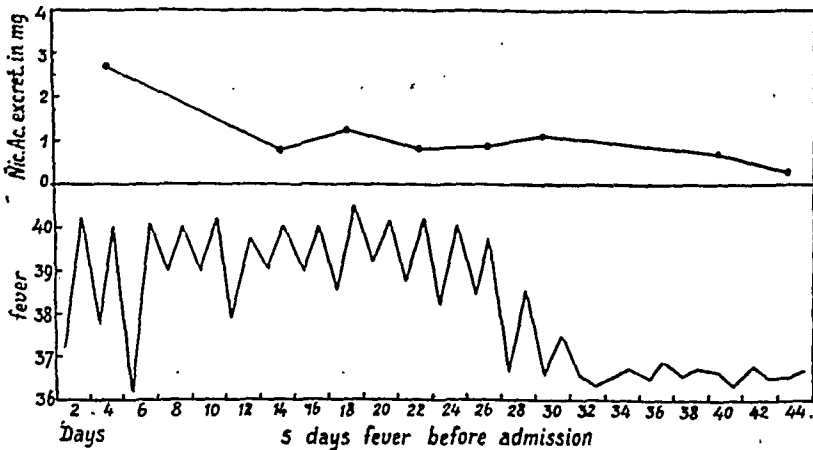


Fig. 3.—Excretion of nicotinic acid in the course of typhoid.

the results of other investigators, who observed no variations in the nicotinic acid content of the blood in various conditions, including pellagra.¹²

12. Carter, P. W., and O'Brien, J. R. P.: Nicotinic Acid Content of Blood in Health and Disease, *Quart. J. Med.* **14**:197 (Oct.) 1945.

vitamin B complex was effective in preventing fatty degeneration. Best and Rideout identified the preventive factor (lipotropic principle) as choline and suggested that the accumulation of fat in the liver was due to a choline deficiency, which resulted in a decreased formation of phospholipids.⁴

Whipple and his co-workers, using dogs, had demonstrated earlier that the sensitivity of the liver to toxins was increased when the protein stores were first depleted and that the ability of the animals to withstand the effects of chloroform anesthesia was decreased.⁵ They found that the sulfur-containing amino acids appeared to exert a pronounced influence in the production of hepatic damage and that they played a key role in the construction of new hepatic proteins as well as in the repair of damaged hepatic cell proteins. They searched for the fraction responsible for this favorable effect and demonstrated methionine to be the most active amino acid.

THE ACTION OF METHIONINE

Early experiments had shown that ingested protein is lipotropic and that the amount of fat found in the livers of animals fed a deficient diet was inversely proportional to the amount of protein and carbohydrate in the diet. György and Goldblatt showed that the addition of choline to a diet low in protein was helpful in the prevention of the deposition of fat and that if cystine was also added hepatic injuries could be entirely prevented.⁶ Tucker and Eckstein found that methionine acted similarly to choline in the prevention of the deposition of fat in the liver.⁷ Later it was found that methionine alone, when added to the diet low in protein, produced the same results as choline plus cystine and that the lipotropic activity of certain proteins was directly proportional to the amount of methionine which they contained. The lipotropic action of methionine was thought to be dependent on its ability to provide methyl groups for the formation of choline.

4. Best, C. H., and Rideout, J. H.: Choline as a Dietary Factor, in Luck, J. M.: Annual Review of Biochemistry, Stanford University, Calif., Annual Reviews, Inc., 1939, vol. 8, pp. 349-370.

5. Miller, L. L.; Ross, J. F., and Whipple, G. H.: Methionine and Cystine, Specific Protein Factors Preventing Chloroform Liver Injury in Protein-Depleted Dogs, *Am. J. M. Sc.* **200**:739-756 (Dec.) 1940.

6. György, P.: Experimental Hepatic Injury, *Am. J. Clin. Path.* **14**:67-88 (Feb.) 1944.

7. Tucker, H. F., and Eckstein, H. C.: The Effect of Supplementary Methionine and Cystine on the Production of Fatty Livers by Diet, *J. Biol. Chem.* **121**: 479-484 (Nov.) 1937.

patients with high fever are given nutrients in amounts just sufficient to maintain normal metabolic requirements, the body is obliged to draw additional amounts from its own stores. During the early stage of the disease the body compensates for the increased demand for nicotinic acid, but as the disease progresses the stores are gradually depleted and the amount available therefore decreases. Toward the end of convalescence, when the body seems to have returned to normal, excretion of nicotinic acid is at its lowest because of the complete depletion of the body's stores.

Nicotinic acid, which as the active element of cohydrogenase is one of the essential metabolites, plays an important role in the metabolism of carbohydrates and of some amino acids. Insufficient intake of nicotinic acid in the course of the disease may therefore have a harmful effect on the functioning of various organs without leading to the full clinical picture of pellagra. These deleterious effects may, however, aggravate the course of the disease and prolong the period of convalescence.

The question arises whether the drop in excretion of nicotinic acid is due specifically to the typhoid infection or merely to the increased metabolism common to all febrile conditions of long duration. This question was not clearly elucidated in the present study for lack of an adequate number of cases of protracted pyrexia other than typhoid for comparison. A similar, though less pronounced, drop in excretion of nicotinic acid was, however, noted in 3 cases (subacute bacterial endocarditis, typhus and pneumonia). On the other hand, in 3 cases of typhus, 8 cases of pneumonia and 1 case of staphylococcic septicemia of two and a half months' duration there were no marked changes in excretion of nicotinic acid. The question of a specific relationship between typhoid and excretion of nicotinic acid therefore requires further investigation.

The increased demand for nicotinic acid demonstrated in our study justifies intensive dietary treatment and even the administration of nicotinic acid and of other synthetic vitamins. We believe that our study represents an additional contribution to recent nutritional investigations which have demonstrated the loss of nutrients during infectious disease, and which have stressed the importance of dietary treatment in shortening the period of convalescence.¹⁵

15. (a) Spies, T. D.; Vilter, R. W., and Douglas, G., Jr.: Nutrition in Convalescence and Rehabilitation; Progress Report, South. M. J. **37**:560 (Oct.) 1944. (b) Malnutrition During Convalescence, Prepared Under Direction of the Committee on the Convalescence and Rehabilitation of the National Research Council, War Med. **6**:1 (Jan.) 1944.

EXPERIMENTAL STUDY

Material.—In the following study 18 patients with hepatic disease received a daily oral supplement of methionine¹⁴ in addition to the usually recommended diet. The patients were divided into three groups.

Group 1 consisted of 4 patients with acute infectious hepatitis. The diagnosis was based on the history of anorexia, malaise, vomiting and fever, the findings of enlargement and tenderness of the liver and the appearance of icterus, shown by laboratory studies to be due to parenchymatous involvement.

Group 2 consisted of 6 patients for whom the diagnosis of chronic hepatitis had been made. All gave a history resembling that of acute infectious hepatitis at the onset but continued to have persistent gastrointestinal complaints as well as clinical and laboratory evidence of hepatic damage for four to six months. Four had marked enlargement of the liver. Three continued to have jaundice of moderate or intense severity and had been treated with diet, vitamins and intravenous administration of dextrose for at least six weeks, without improvement, before the addition of methionine.

Group 3 consisted of 8 patients with chronic hepatitis and ascites (advanced portal cirrhosis of the liver). All had edema, signs of collateral circulation, jaundice and laboratory evidence of hepatic insufficiency. The clinical diagnosis was confirmed by peritoneoscopy and biopsy in 3 patients. Five patients had evidence of enlargement of the liver.

Method.—Alternate patients in groups 1 and 2 and all the patients in group 3 were hospitalized. Both the ambulatory and the hospitalized patients were given a 3,500 calory diet, made up of 120 to 140 Gm. of protein, 130 to 150 Gm. of fat and 350 to 400 Gm. of carbohydrate. Urinalysis and routine studies of the blood, including determination of the hemoglobin content, red blood cell counts, white blood cell counts and differential counts, were done. Sulfobromophthalein and hippuric acid tests and galactose tolerance tests of hepatic function were performed, and the icterus index, prothrombin time, total serum protein content and albumin and globulin fractions were determined. Plasma levels of vitamin A, carotene and ascorbic acid were measured, and the urinary excretion of riboflavin and nicotinic acid was determined. The laboratory methods used have been described in previous publications.¹⁵

If edema was present, the salt intake was restricted, but water was allowed ad libitum. After preliminary study, all patients received therapeutic doses of synthetic B complex vitamins and 3 to 6 Gm. of methionine each day. Hospitalized patients were also given 500 to 1,000 cc. of a 10 per cent solution of dextrose

14. The methionine was furnished by The Upjohn Company, Kalamazoo, Mich.

15. Ruffin, J. M.; Cayer, D., and Perlzweig, W. A.: The Relationship Between the Clinical Picture of a Mild or Early Vitamin Deficiency and Laboratory Determinations of Vitamin Levels, *Gastroenterology* 3:340-356 (Nov.) 1944.

USE OF METHIONINE AND VITAMIN SUPPLEMENTS IN TREATMENT OF HEPATIC DISEASE

Clinical and Laboratory Observations

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WINSTON-SALEM, N. C.

THE CONCEPTS of the origin and therapy of hepatic disease have changed radically in recent years. The belief that cirrhosis is caused by toxic substances, most notably alcohol, is being replaced by the concept that the primary etiologic factor is probably a dietary deficiency or that multiple etiologic agents, acting through a mechanism which produces fatty infiltration of the liver, may be responsible. This concept is supported by the experimental production of cirrhosis in animals deprived of proteins, amino acids and vitamins.

THE EXPERIMENTAL PRODUCTION AND PREVENTION OF HEPATIC DAMAGE AND CIRRHOSIS

The relationship of diet to hepatic damage in laboratory animals has been known for some time. Curtis and Newburgh produced necrosis of the liver in rats by adding as little as 0.75 per cent cystine to a diet low in casein.¹ The severity of the lesions was related to the amount of cystine used. Lillie in 1932 produced further evidence of the dietary origin of cirrhosis by demonstrating fatty degeneration of the liver in rats maintained solely on a diet low in casein.² In 1939 György and Goldblatt described hepatic lesions varying from fatty infiltration and fibrosis to massive necrosis in rats fed a diet deficient in vitamin B complex.³ They were able to prevent the development of these lesions with yeast. This experiment demonstrated the fact that an agent in the

Studies on vitamin levels were done under a grant from the John and Mary R. Markle Foundation.

From the Department of Internal Medicine, Bowman Gray School of Medicine of Wake Forest College, and the North Carolina Baptist Hospital.

1. Curtis, A. C., and Newburgh, L. H.: The Toxic Action of Cystine on Liver of Albino Rat, *Arch. Int. Med.* **39**:828-832 (June) 1927.

2. Lillie, R. D.: Histopathologic Changes Produced in Rats by the Addition to the Diet of Various Amino Acids, *Pub. Health Rep.* **47**:83-93 (Jan. 8) 1932.

3. György, P., and Goldblatt, H.: Observations on the Conditions of Dietary Hepatic Injury in Rats, *J. Exper. Med.* **75**:355-368 (April) 1942.

TABLE 1.—Laboratory Evidence of Hepatic Damage Before and After Treatment with Methionine in Six Patients with Chronic Hepatitis (Group 2)

Case	Vitamin A, International Units		Total Proteins, Gm. per 100 Cc.		Sulfobromophthalein Retention at 30 Minutes, per Cent		Hippuric Acid Excretion, Gm.		Galactose Tolerance, Gm.		Icterus Index, Units		Hemoglobin, Gm.		Enlargement of the Liver	
	Before	After	Before	After	Before	After	Before	After	Before	After	Before	After	Before	After	Before	After
1.....	170	149	5.5	5.4	00	5	3.1	0.8	30	4	14.5	15.5	0	0
2.....	48	92	5.7	6.3	05	15	1.5	...	2.9	0.6	26	15	14.0	14.0	1+	±
3.....	141	142	6.5	6.5	70	0	0.61	2.95	12	8	12.8	14.0	0	0
4.....	78	105	7.8(†)	6.0	70	30	5	5	12.4	12.4	3+	2+
5.....	50	115	5.3	6.2	100	90	1.4	2.9	30	25	14.0	14.0	2+	0
6.....	83	103	7.1	6.4	90	0	1.7	3.0	3.8	1.3	15	10	11.2	11.0	2+	1+

TABLE 2.—Laboratory Evidence of Hepatic Damage Before and After Treatment with Methionine in Eight Patients with Advanced Portal Cirrhosis (Group 3)

Case	Vitamin A, International Units		Total Proteins, Gm. per 100 Cc.		Sulfobromophthalein Retention at 30 Minutes, per Cent		Hippuric Acid Excretion, Gm.		Galactose Tolerance, Gm.		Icterus Index, Units		Hemoglobin, Gm.		Enlargement of the Liver		Ascites	
	Before	After	Before	After	Before	After	Before	After	Before	After	Before	After	Before	After	Before	After	Before	After
1.....	78	136	4.6	0.3	80	70	1.4	3.5	3.6	...	20	10	10.3	11.7	2+	1+	3+	0
2.....	74	82	5.2	0.1	95	40	2.7	...	1.0	1.9	0	10	12.4	11.5	1+	1+	2+	0
3.....	93	75	4.2	5.3	80	10	0.7	0.69	2.9	0.35	10	5	4.7	11	0	0	4+*	2+
4.....	77	115	6.0	5.0	95	40	1.6	1.6	1.6	1.0	20	10	12.5	14.6	1+	1+	2+	0
5.....	125	85	5.2	5.7	80	50	10	10	9.6	9.6	1+	1+	2+*	1+
6.....	5.7	0.5	80	30	1.2	1.0	80	20	12.4	12.4	0	0	3+*	0
7.....	85	68	5.4	6.2	70	70	1.33	0.44	9.6	2.8	15	12	12.4	13.2	3+	3+	1+	1+
8.....	5.9	7.4	70	30	0.47†	0.38	3.04	...	10	10	10.8	...	0	0	4+	2+

* Paracenteses were performed in these cases.

† Value obtained in the intravenous test.

TABLE 3.—Summary of Laboratory Data (Mean Values for Groups 2 and 3)

	Vitamin A, International Units		Total Proteins, Gm. per 100 Cc.		Sulfobromophthalein Retention at 30 Minutes, per Cent		Hippuric Acid Excretion, Gm.		Galactose Tolerance, Gm.		Hemoglobin, Gm.	
	Before	After	Before	After	Before	After	Before	After	Before	After	Before	After
Group 2, chronic hepatitis without ascites (6 patients).....	97	118	6.4	6.2	76	23.5	1.3	3.1	3.3	0.9	13.0	13.5
Group 3, chronic hepatitis with ascites (8 patients).....	71	93	5.3	6.0	79	42	1.5	3.1	3.3	1.4	10.0	11.9

Du Vigneaud elaborated the hypothesis of transmethylation⁸ and suggested that both cystine and choline could be made from methionine by the body and, conversely, that both acted as substitutes for methionine by utilizing the labile methyl groups present in choline. The efficacy of methionine has been shown to be the same whether it is fed as a free amino acid or as a constituent of dietary protein. Apparently the unnatural isomers of methionine can also be utilized by man equally well.⁹

Clinical Application.—Patek in 1937 published a report on the use of a nutritious diet and vitamin supplements in patients with cirrhosis.¹⁰ This diet provided approximately 100 Gm. of protein and 300 Gm. of carbohydrate. The beneficial results noted were attributed to the regeneration of liver parenchyma and the restoration of the function of hepatic cells. Later a diet even higher in protein and supplemented by B complex vitamins and lipotropic substances was found to provide a still more effective method of treatment and often produced remissions even in cases of advanced cirrhosis.¹¹ Previously, when advanced disease of the liver in human beings was manifested clinically by jaundice, evidences of collateral circulation, edema or ascites the process had been considered irreversible and the prognosis extremely grave.

The efficacy of methionine in experimental hepatic damage and cirrhosis has led to its clinical trial. Beattie and Marshall reported that the administration of methionine to patients receiving arsphenamine decreased the incidence of hepatic damage.¹² The same beneficial effects have been observed in patients with acute carbon tetrachloride and trinitrotoluene poisoning. Methionine has been used in patients with infectious hepatitis and cirrhosis, with equivocal results. The limited evidence of its clinical value allows no definite conclusion to be drawn, although the encouraging results obtained appear to justify further clinical trials of methionine.¹³

8. du Vigneaud, V.; Chandler, J. P.; Moyer, A. W., and Keppel, D. M.: The Effect of Choline on the Ability of Homocystine to Replace Methionine in the Diet, *J. Biol. Chem.* **131**:57-76 (Nov.) 1939.

9. Albanese, A. A.: The Utilization of *d*-Amino Acids by Man, *Bull. Johns Hopkins Hosp.* **75**:175-183 (Sept.) 1944.

10. Patek, A. J., Jr.: The Treatment of Alcoholic Cirrhosis of the Liver with High Vitamin Therapy, *Proc. Soc. Exper. Biol. & Med.* **37**:329-330 (Nov.) 1937.

11. Beams, A. J.: The Treatment of Cirrhosis of the Liver with Choline and Cystine, *J.A.M.A.* **130**:190-194 (Jan. 26) 1946.

12. Beattie, J., and Marshall, J.: Methionine in the Treatment of Liver Damage, *Nature, London* **153**:525-526 (April 29) 1944.

13. The Status of Methionine in the Prevention and Treatment of Liver Injury, report of the Council on Pharmacy and Chemistry, *J.A.M.A.* **133**:107 (Jan. 11) 1947.

of dextrose is of added value in patients unable to ingest optimal amounts of carbohydrate.

Transfusions of plasma or whole blood were not found necessary for replacement of hemoglobin and protein in the patients in this series.

Vitamin Supplements.—Since the relationship of nutrition to cirrhosis was demonstrated, it has become customary to give large amounts of B complex vitamins to patients with disease of the liver. Vitamin B complex is of great importance in the mobilization of liver lipids. Handler and Dann, however, have showed that the administration of large doses of nicotinamide to rats produces fatty livers.¹⁶ It has also been suggested that the diseased liver may lose its ability to cope with the persistent demand for methylation.¹⁷ Gillman noted that patients with pellagra who had fatty livers (proved by aspiration biopsy) were less likely to recover when large amounts of nicotinic acid alone were administered than when powdered stomach ("ventriculin") was given.¹⁸

In this study the urinary excretion of nicotinamide and riboflavin was measured before and after a test dose of these vitamins in 3 patients with cirrhosis (group 3) who had not previously received any vitamin supplements. The excretion of riboflavin was within normal limits, but the levels of nicotinamide, as measured by excretion of *N*'methyl-nicotinamide, were two to three times greater than normal. A high incidence of increased excretion of *N*'methylnicotinamide in patients with hepatic damage (as well as in rats poisoned with carbon tetrachloride) has also been noted by Perlzweig and his co-workers. This finding demonstrates the diminished capacity of the damaged liver to utilize and break down nicotinamide.¹⁹

From the information available it would appear that large doses of nicotinic acid in patients with hepatic damage might overtax the methylating ability of the liver and produce increased damage. I have preferred for this reason to use a daily vitamin supplement containing 10 to 15 mg. of nicotinamide rather than the larger amounts usually recommended (100 to 150 mg.). More detailed study of the actual

16. Handler, P., and Dann, W. J.: The Inhibition of Rat Growth by Nicotinamide, *J. Biol. Chem.* **146**:357-368 (Dec.) 1942.

17. Najjar, V. A.; Hall, R. S., and Deal, C. C.: The Methylation of Nicotinamide, *Bull. Johns Hopkins Hosp.* **76**:83-91 (Feb.) 1945.

18. Gillman, T., and others: Substitution of Whole Stomach Extract for Vitamins in Treatment of Malignant Infantile Pellagra, *Nature, London* **154**:210 (Aug. 12) 1944.

19. Perlzweig, W. A.; Huff, J. W., and Rosen, F.: The Effect of CCL₄ Poisoning on the Fate of *N*'Methylnicotinamide in the Rat, *Federation Proc.* **5**: 149 (Feb.) 1946.

intravenously each day. Plasma and blood were not used. Paracentesis was done only if diuretics failed to give relief or when the accumulation of fluid produced respiratory difficulty or inability to eat. Laboratory studies were repeated every seven to ten days on all patients.

Results.—Group 1 (infectious hepatitis): In patients with acute infectious hepatitis, the duration of icterus, gastrointestinal symptoms, and disturbances of hepatic function was apparently unaltered by the methionine supplement. Since the laboratory data and clinical findings during the period of study showed no difference between the control group and those receiving methionine, the detailed results are not tabulated.

Group 2 (chronic hepatitis without ascites): Considerable improvement was noted in each of the 6 patients having chronic hepatitis without ascites (tables 1, 3 and 4). During the one month period of treatment, the values in the hippuric acid test and galactose tolerance test returned to normal. Three patients continued to show retention of sulfobromophthalein, but to a lesser degree. The total serum protein contents were unchanged. The mean plasma levels of vitamin A rose from 97 to 118 international units.

Two patients who were jaundiced had been treated in other hospitals with diet and vitamin supplements, without improvement. Within seven days after the addition of methionine, both noted an increase in appetite and subsidence of nausea, bloating and malaise. The icterus cleared rapidly. When medication was temporarily discontinued after one month, both patients stated that they could note a difference in their feelings and requested that they again be given methionine.

This group (both the ambulatory and the hospitalized patients) showed the most rapid subjective and objective response to treatment. The interval before improvement was noted was the same in the 2 patients who had received previous treatment without methionine as in the patients whose treatment was begun with methionine.

Group 3 (chronic hepatitis with ascites, or advanced portal cirrhosis): Evidences of decreased hepatic function were most notable in this group. All studies of hepatic function indicated some improvement during the period of study, although evidence of impaired function continued (tables 2 and 3). The serum protein rose from a mean of 5.3 Gm. per hundred cubic centimeters to 6.0 Gm., and a mean rise of 10 per cent in hemoglobin was also noted. The vitamin A level showed a rise of similar degree. Of the 8 patients, 7 were improved after an average treatment interval of one month (table 4). One patient who had had recurrent ascites requiring several parenterases during the previous year was able to return to work as a railroad engineer and has remained well. In 2 patients who had jaundice as well as ascites, abdominal fluid and icterus

treatment of infectious hepatitis, without demonstrable benefit.²⁰ The duration of jaundice, the enlargement and tenderness of the liver, the gastrointestinal symptoms and the period of hospitalization were not altered.

Methionine in Chronic Hepatitis: Among the patients with chronic hepatitis, the greatest improvement was noted in those without ascites (group 2), as might be expected. All patients with chronic hepatitis without ascites showed progressive improvement and were able to return to full activity. Three of 6 patients had been hospitalized previously and had received a diet high in protein and low in fat, accessory vitamins and intravenous injections of dextrose, without improvement; all 3 showed immediate improvement after the addition of methionine to the therapy. In 2 of these 3 patients the livers were not palpable. The remaining 4 patients in this group had moderate to pronounced hepatic enlargement, which showed some regression during the period of treatment. The presence or absence of enlargement of the liver per se did not appear to affect the prognosis with the use of methionine.

The prompt and uniform clinical improvement in these patients, particularly in those who had previously been treated by accepted methods, is of considerable interest. Unfortunately, there is little in the way of controlled laboratory and clinical data on the results of the treatment of chronic hepatitis with diet, vitamins and lipotropic substances. Morrison reported a clinical study on a group of 11 patients with chronic hepatitis who received methionine and choline in addition to a diet high in proteins and in carbohydrates, vitamins and liver extract. He felt that the addition of methionine had definite therapeutic value when the results were compared with those obtained in a group of 9 patients treated earlier without lipotropic substances.²¹

Methionine in Chronic Hepatitis with Ascites: The uniformly poor prognosis in cirrhosis after ascites appears has been noted in many excellent studies of the natural history of this disease. In a series of 150 patients seen at the Mayo Clinic between 1930 and 1938 and treated with a diet high in carbohydrate and low in protein and in fat, mercurial diuretics, intravenously administered dextrose, limitation of fluids and paracenteses, 68.8 per cent did not survive a year.²² Ratnoff and Patek, reporting on a series of 386 patients, also found that more than

20. Wilson, C.; Pollock, M. R., and Harris, A. D.: Therapeutic Trial of Methionine in Infective Hepatitis, *Brit. M. J.* 1:399-401 (March 24) 1945.

21. Morrison, L. M.: The Response of Cirrhosis of Liver to an Intensive Combined Therapy, *Ann. Int. Med.* 24:465-478 (March) 1946.

22. Fleming, R. G., and Snell, A. M.: Portal Cirrhosis with Ascites: An Analysis of Two Hundred Cases with Special Reference to Prognosis and Treatment, *Am. J. Digest. Dis.* 9:115-120 (April) 1942.

completely disappeared; they were able to return to full time work within two months and have remained well. Three patients showed an increase in strength and appetite together with regression of ascites but were unable to return to active work. One patient who also had arteriosclerotic heart disease with congestive failure showed no response to treatment but went progressively downhill and died. The remaining patient showed moderate improvement and returned to work, but he died after an initial massive gastrointestinal hemorrhage.

TABLE 4.—*Clinical Results*

	Group 2 Chronic Hepatitis Without Ascites (6 Patients)	Group 3 Chronic Hepatitis with Ascites (8 Patients)
Showed improvement in signs * and symptoms †	6	7
Able to resume full activities.....	6	3
Did not improve or died.....	0	2 died, 1 of massive hemor- rhage after returning to work and 1 of arteriosclerotic heart disease with congestive failure and hepatic insufficiency ‡
Average duration of follow-up.....	14 mo.	13 mo.

* Decrease in edema, ascites, anorexia, size of liver and jaundice.

† Increase in appetite, strength and well-being.

‡ Death occurred after three months.

COMMENT

Diet.—The importance of a nutritious diet high in protein and carbohydrate is well recognized in the treatment of disease of the liver. Such a diet was given in multiple small feedings to all the patients in this study, and in most instances it was well and completely taken. Amino acid solutions were given to 4 patients, but the unpleasant taste of the mixtures tended to limit their oral use. No additional benefit was noted in 3 patients who received amino acids parenterally; apparently this method of administration did not provide more complete utilization or result in a greater increase in plasma protein formation. One patient who was receiving a protein hydrolysate intravenously showed a generalized erythematous follicular eruption. When severe hepatic insufficiency is present, the administration of incomplete protein digests is probably contraindicated, since they may be poorly handled by the damaged liver.

The beneficial effects of a high carbohydrate intake in patients with hepatic disease are generally accepted. It is felt that carbohydrates are important chiefly for their protein-sparing capacity. In addition, the storage of glycogen in the liver appears to limit fatty infiltration. Since glycogen is stored in damaged livers only when the blood sugar levels are high, the intravenous administration of a 5 to 10 per cent solution

Progress in Internal Medicine

SYPHILIS

A Review of the Recent Literature

FRANK W. REYNOLDS, M.D.

AND

JOSEPH EARLE MOORE, M.D.

BALTIMORE

IN THIS annual review¹ of recent developments in the field of syphilology emphasis is placed on subjects of greatest current importance. In publications appearing from July 1946 to June 1947 that emphasis is on therapy, particularly with penicillin, the limitations of which are gradually becoming apparent. There also is evident a rising tide of protest against the low specificity of current serodiagnostic tests, recently brought into sharper focus by mass testing of the blood of millions of persons by Selective Service, the American Red Cross and the armed forces separation centers. Few original articles on the fundamental problems of syphilis have appeared.

NEW BOOKS

Two clinical manuals on the venereal diseases have appeared during the period covered by this review. Lomholt's book² is an English

From the Venereal Disease Division of the Medical Department, The Johns Hopkins University School of Medicine.

1. (a) Moore, J. E.: Syphilis: A Review of the Recent Literature, *Arch. Int. Med.* **56**:1015 (Nov.) 1935. (b) Padget, P., and Moore, J. E.: Syphilis: A Review of the Recent Literature, *ibid.* **58**:901 (Nov.) 1936; (c) **60**:887 (Nov.) 1937. (d) Padget, P.; Sullivan, M., and Moore, J. E.: Syphilis: A Review of the Recent Literature, *ibid.* **62**:1029 (Dec.) 1938. (e) Moore, J. E., and Mohr, C. F.: Syphilis: A Review of the Recent Literature, *ibid.* **64**:1053 (Nov.) 1939. (f) Mohr, C. F.; Padget, P., and Moore, J. E.: Syphilis: A Review of the Recent Literature, *ibid.* **66**:1112 (Nov.) 1940. (g) Mohr, C. F.; Padget, P.; Hahn, R. D., and Moore, J. E.: Syphilis: A Review of the Recent Literature, *ibid.* **69**:470 (March) 1942. (h) Reynolds, F. W.; Mohr, C. F., and Moore, J. E.: Syphilis: A Review of the Recent Literature, *ibid.* **70**:836 (Nov.) 1942; (i) **72**:635 (Nov.) 1943. (j) Mohr, C. F.; Scott, V.; Hahn, R. D.; Clark, E. G., and Moore, J. E.: Syphilis: A Review of the Recent Literature, *ibid.* **74**:390 (Nov.) 1944. (k) Mohr, C. F.; Scott, V.; Hahn, R. D., and Moore, J. E.: Syphilis: A Review of the Recent Literature, *ibid.* **77**:332 (March); 428 (April) 1946. Reynolds, F. W., and Moore, J. E.: Syphilis: A Review of the Recent Literature, *ibid.* **78**:592 (Nov.); **78**:733 (Dec.) 1946; **79**:92 (Jan.) 1947.

2. Lomholt, S.: Venereal Diseases in General Practice, London, H. K. Lewis & Co., Ltd., 1946.

vitamin needs and the degree of utilization in patients with hepatic disease is indicated.

Although many of the patients were found to have lowered plasma levels of vitamin A, the values for the most part fell in the low normal range. These comparatively low levels were probably dependent on decreased intake and absorption and on accumulation in the fatty liver. It is well recognized that in patients with hepatic disease low levels of vitamin A in the plasma may exist without signs of a frank deficiency. Nothing to indicate any clinical deficiency of vitamin A was noted in the patients in this series, and it was not felt that administration of accessory vitamin A was indicated.

In most of the patients, plasma levels of ascorbic acid were also within low normal limits, and no supplementary vitamin C was administered.

Vitamin K was given only to patients whose stools contained no bile and in whom a prothrombin deficiency could be demonstrated. In such patients the prothrombin time returned to normal within one to two days after the injection of 1 mg. of vitamin K or in two to three days if 1 mg. of vitamin K and 1 Gm. of the bile salts were administered orally each day.

Methionine.—Since methionine appears to be the amino acid most essential for normal hepatic function and since it acts to prevent the deposition of fat in the liver as well as to protect the liver against nutritional deficiencies and hepatotoxic agents, supplementary doses of methionine would seem to be justified in the treatment of patients with hepatic damage. The use of a single substance rather than a combination of choline and cystine has the advantage of simplicity and obviates any danger associated with the possible toxicity of cystine. The administration of adequate amounts of methionine by diet alone may be difficult in patients who have anorexia, since they may be unable to ingest the necessary amounts of food. Casein is the richest dietary source of methionine, but approximately 1 gallon (3.7 liters) of milk would be required to supply 3 Gm. of methionine. In addition, there is some evidence that dietary methionine is more subject to utilization for purposes other than repair of the liver.

The patients in this series were given supplements of methionine orally in doses of 3 to 6 Gm. per day, without harmful effects. The larger doses did not appear to provide any added benefits.

Methionine in Acute Infectious Hepatitis: No improvement which could be attributed directly to methionine was noted in the patients with early infectious hepatitis. This finding confirms the work of other authors, who have used as much as 7.5 Gm. of methionine daily in the

noted in further support of this suspicion that Fracastorius wrote two pathetic plays about the death of his children. The idea receives further support from an unknown Paduan biographer who states that "Fracastorius had a round face, black eyes and a nose that became flat from prolonged contemplation of the stars." That the poet was not born with this nasal deformity is attested by the fact that earlier portraits did not picture him thus.

Dujardin⁷ seeks to trace the origin of the term syphilis back beyond the time of Fracastorius to ancient Greek mythology. According to this author, the root word was first used by Ovid, from whom Fracastorius drew heavily in writing his famous poem. Ovid related the story of Niobe, who because of her pride was turned to stone after her children (one of whom was named "Sipyle") had been killed by Apollo. Ovid himself apparently got his material from a tale of Apollodorus (140 B. C.), who in turn may have drawn his inspiration from Homer (ninth century, B. C.). Homer mentions a Mount Sipyle in Asia Minor which to those with imagination has the appearance of a woman of sorrow, her tears (mountain streams) falling on rock formations which are not unlike the bodies of dead infants at the feet of their mother. The modern spelling of the word syphilis is thought to have originated from an error on the part of Ovid's copyists.

The Origin of Syphilis.—Entering into the controversy concerning the origin of syphilis, Wiedmann⁸ sides with those who believe that the disease was present in Europe long before the return of Columbus from the New World. This author finds veiled references in the writings of the ancient Greeks, Romans and Hebrews to an "unclean disease" of the genitalia which at times was confused with leprosy and the venereal nature of which apparently was not suspected. There is also evidence, he thinks, that a disease characterized by a cutaneous rash and pains in the joints was present among the inhabitants of Western Europe before the days of Columbus' voyages. To explain the sudden outbreak of virulent syphilis in Europe in the last decade of the fifteenth century, he points out that epidemics not infrequently follow in the wake of war and that in those days Europe was torn by the armies of Charles VIII.

Some of the highlights in the history of syphilis have been described by LeVan,⁹ whose article gives in tabular outline the conflicting data utilized by those who support the theory of the American origin of syphilis and those who believe that the disease was present in Europe prior to the discovery of the New World.

7. Dujardin, B.: Origine du mot syphilis, Presse méd. 55:11 (Jan. 4) 1947.

8. Wiedmann, A.: Ueber den Ursprung der Syphilis, Wien. klin. Wchnschr. 59:281 (May 9) 1947.

9. LeVan, P.: Highlights of the History of Syphilis, J. Social Hyg. 33:249 (June) 1947.

60 per cent died within a year after the first symptoms of the disease.²³ The spontaneous loss or absorption of ascitic fluid occurred in only 7 per cent of the cases. With the use of the supplemental diet and accessory vitamins, 60 per cent showed a disappearance of ascites and 20 per cent showed signs of clinical recovery. These carefully followed studies serve as a clinical control for the cases here reported in group 3.

While it is admittedly unwise to draw conclusions from the small number of cases reported in this paper, the response of the patients with chronic hepatitis, both with and without ascites, seems worthy of note. Of 8 patients with advanced cirrhosis, 3 who had jaundice and ascites have been clinically well and able to carry on full time work for an average duration of thirteen months after treatment. Three others are still alive but are forced to restrict their activity; 1 of these requires occasional paracenteses. Both the clinical and the laboratory data, however, indicate that these 3 patients improved under treatment with methionine.

SUMMARY

During the past decade the changes in the therapy of patients with chronic disease of the liver have greatly altered the prognosis for such persons. The underlying defect in many instances appears to be the accumulation of fat in the liver cells as a result of dietary deficiencies, infection or hepatotoxins.

The use of vitamin supplements and a high calorie diet containing increased amounts of protein and carbohydrate is important in mobilizing the lipids of the liver, repairing hepatic damage and restoring hepatic function.

Experimental as well as clinical observations indicate that the administration of excessively large amounts of nicotinamide may further decrease the methylating ability of the damaged liver and is unwise in view of the diminished ability of the liver to utilize and break down this vitamin.

The efficacy of methionine in the prevention and treatment of experimental hepatic injury appears to justify its clinical use. When given orally in daily doses of 3 Gm. to the patients in this series, it appeared to be most beneficial in cases of chronic hepatitis without ascites. No beneficial effect was noted in patients with acute infectious hepatitis.

23. Ratnoff, O. D., and Patek, A. J., Jr.: Natural History of Laennec's Cirrhosis of Liver: Analysis of Three Hundred Eighty-Six Cases, *Medicine* **21**:207-268 (Sept.) 1942.

only because many different spirochetes have been described but also because in many cases there is lack of agreement among various authors as to the proper naming and classification of the organisms studied.

Robinson and Wichelhausen¹² point out the inadequacy of the available means for identification and classification of oral spirochetes and describe a method by which "specific" antigen extracts may be prepared from cultured spirochetes. Utilizing this method with immune serums, the authors differentiate sixteen strains of morphologically and culturally identical oral spirochetes into five groups. Two strains of oral spirochetes were found which were serologically identical with the Reiter and Kazan strains but serologically different from smaller oral spirochetes and from the Nichols and Noguchi strains of *T. pallidum*. The Nichols and Noguchi strains were shown to be serologically related to each other but both serologically and morphologically different from the Reiter and Kazan strains and serologically different from several strains of oral spirochetes. It is still an open question whether the serologic "groups" described actually represent different species of spirochetes or whether they indicate the existence of subtypes. The first interpretation is supported by the fact that precipitin tests apparently differentiate morphologically dissimilar spirochetes and the latter by the apparent differentiation of morphologically similar organisms and by the large number of different types thus demonstrated.

Hampp¹³ has made agglutination studies, using oral spirochetes including *Borrelia Vincenti* and cultured strains of nonpathogenic *T. pallidum*. Injected intravenously into rabbits, all these spirochetal organisms evoked homologous agglutinins in high titer.

EXPERIMENTAL SYPHILIS

Experimental Syphilis in Mice.—Wile¹⁴ reports that experimental syphilis in mice inoculated with the Nichols strain of *T. pallidum* remains an occult infection even after four successive passages. Dark field examinations, Warthin-Starry stains and hematoxylin-eosin preparations failed to demonstrate *T. pallidum* or any characteristic histopathologic changes in mouse tissues which were demonstrably infectious in rabbits. After successive passages, the pooled spleens, livers and gonads of mice retained their infectiousness for rabbits longer than did the brain tissues.

12. Robinson, L. B., and Wichelhausen, R. H.: The Problem of Identification of Oral Spirochetes and Description of a Precipitin Test for Their Serological Differentiation, *Bull. Johns Hopkins Hosp.* **79**:436 (Dec.) 1946.

13. Hampp, E. G.: Agglutination Studies of the Smaller Oral Treponemes, *Borrelia Vincenti* and Cultured Strains of *Treponema Pallidum*, *J. Am. Dent. A.* **34**:606 (May) 1947.

14. Wile, U. J.: Transmission of Experimental Syphilis from Mouse to Mouse: Absence of *Spirochaeta Pallida* and of Pathologic Changes in Presence of Successful Inoculation, *Am. J. Syph., Gonorr. & Ven. Dis.* **31**:109 (March) 1947.

edition of the Danish textbook which has been used widely throughout the Scandinavian countries. Delayed in publication because of the German occupation of Denmark, the book now is out of date, not so much in the discussions on the clinical manifestations of syphilis as with respect to the discussions on therapy. The clinical aspects of early syphilis are well covered and beautifully illustrated; the late manifestations of the disease, aside from the benign late lesions of the skin, are conspicuously slighted. Marshall's textbook³ is an elementary treatise designed for general practitioners and medical students. As such, it fulfils its purpose, but to those especially trained in syphilology there are readily discernible shortcomings, especially with respect to the more modern aspects of syphilotherapy.

Vonderlehr and Heller⁴ are the authors of a detailed and comprehensive account of the history of the control of venereal disease and of the newer procedures employed in the fight against the genitoinfectious diseases. Each of the authors has served as chief of the Venereal Disease Division of the United States Public Health Service, and each has been intimately associated with the wartime development of venereal disease control. Their experience eminently qualifies them to write authoritatively on venereal disease control in all its many ramifications.

Moore's monograph⁵ on penicillin in syphilis is the first detailed summary of the results of the nationwide cooperative study of penicillin therapy in syphilis, with which the author has been intimately associated. Nearly half of the text is devoted to fundamental information on the chemistry, pharmacology and experimental therapeutics of penicillin. The rest of the monograph discusses the clinical applications of penicillin in various phases of syphilis.

HISTORY OF SYPHILIS

Origin of the Word "Syphilis."—Fracastorius, famous poet, astronomer and physician of the Italian Renaissance, is responsible for the introduction of the word "syphilis." In his pastoral poem "Syphilis Sive Morbus Gallicus," composed some twenty years after the appearance of the disease in epidemic form on the European continent, the hero was a shepherd named "Syphilus."

Solente⁶ finds Fracastorius' description of the disease so accurate and so touchingly sincere that he suggests that perhaps the poet actually was describing his own symptoms as a victim of syphilis himself. It is

3. Marshall, J.: *The Venereal Diseases: A Manual for Practitioners and Students*, New York, The Macmillan Company, 1946.

4. Vonderlehr, R. A., and Heller, J. R., Jr.: *The Control of Venereal Disease*, New York, Reynal & Hitchcock, Inc., 1946.

5. Moore, J. E.: *Penicillin in Syphilis*, Springfield, Ill., Charles C Thomas, Publisher, 1946.

6. Solente, G.: *Le nom de syphilis et son mystère: Essai de solution*, Presse méd. 48:663 (Oct. 5) 1946.

Comparing the experimental disease produced in the rabbit by intratesticular inoculation with *T. cuniculi* with the manifestations produced by similarly inoculated *Treponema pallidum* and *Treponema pertenue*, McLeod and Turner¹⁷ report that the reactions produced in the animal host by the three species of organisms have many features in common; lesions develop in somewhat the same sequence and bear a superficial resemblance to one another, and the serologic response is much the same in the three diseases. Nevertheless, differences in the appearance of the individual lesions and in the progression of the disease were observed, and the differences between one group and another were far greater than the differences among the animals of any one group. The authors ascribe these variations to factors inherent in substantial biologic differences in the infecting organisms rather than to those inherent in the host or the environment.

SERODIAGNOSIS OF SYPHILIS

Syphilitic Reagin.—In 1938 Marrack¹⁸ summarized the accumulated data on the chemical and physical properties of antibodies and concluded that no convincing evidence of measurable differences between antibody globulins and globulin fractions normally present in serum had been adduced. The evidence at that time seemed to indicate that the only differences were the specific reactivity of antibodies with the appropriate antigens and possibly an increased resistance of the reactive groupings to the action of proteolytic enzymes.

The recent experiments of Henriksen¹⁹ support this conclusion. This investigator has shown that when the floccules formed by the interaction of beef heart antigen and syphilitic serum are injected into rabbits two different antibodies are produced; one is directed against the lipid antigen of the beef heart extract and the other against syphilitic antibody. Since the second antibody reacted as well with normal human serums as with strongly positive syphilitic serums, it is concluded that "the specificity of syphilitic antibody seems to be the same as that of certain normal serum globulins."

That syphilitic reagin possesses antigenic properties has also been shown by Laporte, Pérez and Hardré de Looze.²⁰ These investigators

17. McLeod, C., and Turner, T. B.: Studies on the Biologic Relationship Between the Causative Agents of Syphilis, Yaws and Venereal Spirochetosis of Rabbits: II. Comparison of the Experimental Disease Produced in Rabbits, *Am. J. Syph., Gonorr. & Ven. Dis.* **30**:455 (Sept.) 1946.

18. Marrack, J. R.: *The Chemistry of Antigens and Antibodies*, London, His Majesty's Stationery Office, 1938.

19. Henriksen, S. D.: The Antigenic Specificity of Syphilitic Antibody Globulin, *J. Immunol.* **55**:153. (Feb.) 1947.

20. Laporte, R.; Pérez, J. J., and Hardré de Looze, L.: Sur les propriétés antigéniques de la réagine syphilitique, *Ann. Inst. Pasteur* **72**:678 (July-Aug.) 1946.

Syphilis and Henry VIII.—There has long been speculation among historians of the Tudor period in England as to whether Henry VIII contracted syphilis and transmitted it to his wives and descendants. Some medical authorities are inclined to think this is a plausible explanation of Henry's numerous matrimonial misfortunes in search of a male heir and base their opinion on the following facts: (1) Henry's lusty sexual appetite; (2) the extraordinary number of premature and dead children born to two of his wives (Catherine of Aragon and Anne Boleyn); (3) the suspicious frontal bossing apparent in portraits of his daughter Mary; (4) the physical, mental and moral degeneration that he displayed in early middle life; (5) the fact that his legs became "swollen and covered with festering sores, causing an unbearable stench," and (6) the draining sinus on his leg, which conceivably could have been osseous syphilis.

In an entertaining article Ellery¹⁰ controverts these factors as indications of syphilis in the corpulent Henry. Indicating that this king's sexual promiscuity may have been overly stressed, he suggests that Henry's wives' miscarriages and stillbirths may have been due to his choosing Rh-negative women for his first two wives, that the leg ulcers may have been either varicose or osteomyelitic, that the weight of evidence is against both dementia paralytica and tabes dorsalis and that since Henry was somewhat neurasthenic his dread of disease would have led him to undergo the traditional treatment of that day, which consisted of sweating and the administration of mercury until salivation was induced.

Patterson¹¹ concedes several of these arguments but points out that the obstetric histories of Catherine and Anne Boleyn, both of whom had several miscarriages or stillbirths before bearing living children, are more suggestive of syphilis than Rh incompatibility and that the statistical improbability of Henry's having chosen in succession two Rh-negative mates makes this explanation unlikely. He writes: "Syphilis was rampant in Henry's day, and, knowing what we do of Henry's bed-time habits, he must have been singularly fortunate to have escaped the ubiquitous spirochaete. In fact, if Henry VIII did not have syphilis, he jolly well deserved to."

TREPONEMA PALLIDUM AND RELATED ORGANISMS

Oral Spirochetes.—Classification and identification of spirochetes found in the oral cavity and in the respiratory tract have been based largely on their morphologic characteristics. Confusion has arisen not

10. Ellery, R. S.: Must Syphilis Still Serve? *M. J. Australia* 1:391 (March 29) 1947.

11. Patterson, H. S.: Must Syphilis Still Serve? Correspondence, *M. J. Australia* 1:514 (April 19) 1947.

Kline²⁴ again reports favorably on the cardiolipin-lecithin antigen, which he has found to give more specific results in the microscopic slide precipitation test in nonsyphilitic patients than Eagle, Hinton, Kahn, Kline and Mazzini antigens and more sensitive results in patients with syphilis than Hinton, Kahn and Kline antigens. Evidence is presented to demonstrate a greater specificity of cardiolipin-lecithin antigen in persons with malaria and in normal persons. That this antigen is not absolutely specific for syphilitic reagin is evidenced by the occurrence of occasional positive reactions in nonsyphilitic patients and in patients with leprosy. The excellent results obtained with cardiolipin-lecithin antigen and the simplicity of the slide flocculation technic cause the author to recommend the two as a basis for a single standard serologic test for syphilis worthy of universal adoption.

Brown²⁵ describes a quantitative macroprecipitation test for syphilis which utilizes a purified antigen composed of cardiolipin, lecithin and cholesterol. Comparing the test with quantitative complement fixation procedures, she found it to give results that reflect the course of syphilitic infection and the response to treatment.

However good serologic tests employing cardiolipin antigens may be, their specificity is not absolute. Stout²⁶ reports that in both complement fixation tests and flocculation tests performed with these antigens positive reactions occur in presumably nonsyphilitic donors in cases of (1) malaria, (2) infectious mononucleosis and (3) infections of the upper respiratory tract. False positive reactions also were observed in persons presumably nonsyphilitic and with no evidence of any disease whatsoever.

Wassermann Tests on Anticomplementary Serum.—Taran²⁷ describes a technic which he believes permits the satisfactory performance of a Wassermann test on anticomplementary serum. The procedure is based on the saturation of the serum with undiluted complement to satisfy the "fixing" properties of the serum. The excess complement then is destroyed and a Wassermann test performed in the usual manner. With known negative and positive serums the results with this technic were the same with complement saturation as without it. With anticomplementary serums there was good correlation between

24. Kline, B. S.: Cardiolipin-Lecithin Antigen: Recent Development Toward a Single Standard Test of the Blood for Syphilis, *Arch. Dermat. & Syph.* **55**:514 (April) 1947.

25. Brown, R.: A Quantitative Macroprecipitation Test for Syphilis with the Cardiolipin-Lecithin-Cholesterol Antigen, *Am. J. Syph., Gonorr. & Ven. Dis.* **31**:304 (May) 1947.

26. Stout, G. W.: Reactivity of Tests Using Cardiolipin Antigen in a Limited Number of Nonsyphilitic Cases, *Am. J. Syph., Gonorr. & Ven. Dis.* **31**:314 (May) 1947.

27. Taran, A.: A Simple Method for Performing a Wassermann Test on Anticomplementary Serum, *J. Lab. & Clin. Med.* **31**:1037 (Sept.) 1946.

In a series of experiments Stratton¹⁵ transferred brain, lymph nodes and spleen from mice infected with syphilis directly from mouse to mouse three times without an intervening host such as a rabbit being used. The infectivity of all organs was ascertained at each transfer by inoculation into the testes of rabbits. Only on the first transfer were brain and spleen tissues infectious, but from the lymph nodes virulent organisms were recovered on all transfers. In another study lymph nodes from rabbits and brains, lymph nodes and spleen from mice infected with syphilis were frozen and maintained at a temperature of -78°C . At the end of a year the lymph nodes from rabbits and the brains from mice had lost their infectivity. The virulence of lymph nodes from mice appeared to have been attenuated, but the infectivity of mouse spleen was not impaired.

Venereal Spirochetosis of Rabbits.—There is in rabbits a naturally occurring spirochetal disease, the causative agent of which, *Treponema cuniculi*, is morphologically indistinguishable from the spirochetes of syphilis and yaws. In this rabbit infection lesions occur principally in the genital region, and the disease is believed to be transmitted from rabbit to rabbit by sexual contact.

Under experimental conditions rabbits may also be infected with *T. cuniculi* by intratesticular inoculation. McLeod and Turner,¹⁶ who have studied experimental venereal spirochetosis, found that local and generalized lesions, positive reactions to serologic tests and a degree of immunity to reinoculation with the same species of organism that resembles that of experimental syphilitic infections develop in rabbits. Lesions produced by *T. cuniculi* likewise respond to treatment with neoarsphenamine. Individual lesions differed strikingly from those of experimental syphilis in their lack of the degree of induration so commonly observed in this disease. Multiple minute granulomas of the parietal tunic of the testis were observed and are considered to be peculiar to the condition. Lesions of the skin and appendages occurred in great profusion in some rabbits, but these lesions also differed from the cutaneous manifestations of experimental syphilis. Histologically, the lesions were characterized by areas of infiltration of lymphocytes, monocytes and plasma cells, much as is observed in yaws and syphilis. Lesions of the bones or involvement of the cornea of the eye were not observed among over 200 rabbits experimentally infected with *T. cuniculi*. The popliteal lymph nodes were shown to harbor treponemes during both the active and the clinically latent stage of the disease.

15. Stratton, E. K.: Preservation of Virulence of *Treponema Pallidum*: Some Additional Laboratory Methods, *Arch. Dermat. & Syph.* **54**:25 (July) 1946.

16. McLeod, C., and Turner, T. B.: Studies on the Biologic Relationship Between the Causative Agents of Syphilis, Yaws and Venereal Spirochetosis of Rabbits: I. Observations on *Treponema Cuniculi* Infection in Rabbits, *Am. J. Syph., Gonorr. & Ven. Dis.* **30**:442 (Sept.) 1946.

known to older serologists, which is that serologic tests for syphilis may be performed under technical conditions which will elicit positive reactions in most nonsyphilitic persons. These "universal serologic reactions" may be elicited by serum-lipid antigen combinations under a variety of conditions, low sodium chloride concentration and low temperature being especially favorable to the occurrence of a positive reaction to flocculation tests in normal persons. The sensitivity of the tests may be increased or decreased in numerous ways. Wheeler, Brandon and Kahn,³¹ for example, have demonstrated antagonistic effects of cephalin and lecithin on the Kahn antigen. Cephalin was found to increase sensitivity, whereas lecithin caused a decrease, making possible "correction of antigen" in either direction. Many extraneous factors appear to influence the results of serologic procedures. The experiments of Breazeale and Dunn³² suggest that even exposure of serum specimens to sufficient concentrations of tobacco smoke may influence the accuracy of serologic tests for syphilis. It is reported that in the presence of tobacco smoke the "titer" of syphilitic serum was increased slightly.

Miller³³ contrasts the simplicity of interpretation of the serologic tests in use thirty years ago with the difficulties inherent in the adjudication of the results of the multiplicity of the highly sensitive tests in use today. Outlining a suggested method of approach to the clinical study of false positive reaction to serologic tests, he recommends that the physician should suspect a false positive result if (1) reactions are weakly positive or doubtful, (2) there are discrepancies between the results of flocculation tests and those of complement fixation tests, (3) reactions to confirmatory tests are positive only in low titer or fluctuant in degree of positivity or (4) reactions to serologic tests become or tend to become negative within a period of three months in the absence of treatment.

Serologic Surveys.—Wolman³⁴ has surveyed the significance of 783 positive Kahn reactions as encountered in a population of 82,070 male enrollees in the United States Maritime Service. His study indicates that 40 per cent of these men had single positive reactions of

31. Wheeler, A. H.; Brandon, E. M., and Kahn, R. L.: The Effect of Lipids on Kahn Antigen: I. Reduction of Sensitivity by Addition of Lecithin, *Am. J. Clin. Path.* **17**:117 (Feb.) 1947; II. Increase of Sensitivity by the Addition of Cephalin, *ibid.* **17**:130 (Feb.) 1947.

32. Breazeale, E. L., and Dunn, C. W.: Effect of Tobacco Smoke on Kahn and Hinton Reactions, *Arizona Med.* **3**:239 (July) 1946.

33. Miller, A. L., Jr.: Biologically False-Positive Wassermann Tests in Non-Syphilitic Patients, *New Orleans M. & S. J.* **99**:335 (Jan.) 1947.

34. Wolman, I. J.: Positive Reaction to the Kahn Test for Syphilis: Their Incidence and Meaning in Healthy American Men; a Survey of 82,070 U. S. Maritime Service Enrollees, *Am. J. M. Sc.* **212**:280 (Sept.) 1946.

injected into rabbits the floccules obtained by the interaction of Meinicke antigen and syphilitic serum and were able to demonstrate the development in the blood of the rabbits of an antibody.

Specificity of Serologic Precipitation.—The process of serologic precipitation is customarily described as a sequence of these two phases: a rapid primary phase involving combination of antigen and antibody molecules and a slower secondary phase in which the initial molecular complexes aggregate. The second phase is manifested by the development of opalescence and by the formation and sedimentation of macroscopic particles of precipitate. It is generally agreed that the primary phase is characterized by a high degree of serologic specificity; indeed, the specificity of this phase constitutes a fundamental theorem in modern immunochemistry. There is, however, no universal agreement regarding the character of the forces which operate in the secondary phase.

Lanni,²¹ in a series of precipitative mixing experiments conducted with the aid of a turbidimeter and a dark field microscope, concludes that serologic precipitation is governed largely by a highly specific mechanism except in the terminal period, when the operation of nonspecific forces becomes apparent. His findings are used as the basis for a new description of precipitation in terms of the formation and aggregation of elementary particles of specific precipitate called seromicrons.

Cholesterolized Antigens.—Anttonen²² has made an extensive study of the results of complement fixation tests, comparing the results obtained from Wassermann antigens with the addition of a cholesterol sensitizer with those obtained without the sensitizer. He concludes that the cholesterolized antigen is significantly superior in sensitivity to compensate for the slight decrease in specificity that attends its use.

Cardiolipin Antigen.—The requisites for a satisfactory routine serologic test for syphilis as outlined by Harris, Rosenberg and Riedel²³ are that such a test be (a) standardized, (b) reproducible, (c) susceptible of rapid performance by a simple technic and (d) characterized by a high degree of sensitivity and specificity. In a preliminary evaluation of serologic tests performed with cardiolipin-lecithin antigens, the authors report "encouraging" results in all these respects. They present their data without comment since they consider them "to be insufficient evidence on which to base an opinion of adequacy."

21. Lanni, F.: The Specificity of Serologic Precipitation, *J. Exper. Med.* **84**: 167 (Aug.) 1946.

22. Anttonen, V. M.: Ueber die Verstärkung der Wassermannschen Reaktion durch Zusatz verschiedener Cholesterine zum Rinder-herzantigen und über die unspezifischen serologischen Luesreaktionen, Kuopio, Oy. Kuopion Kansallinen Kirjapaino, 1945.

23. Harris, A.; Rosenberg, A. A., and Riedel, L. M.: A Microflocculation Test for Syphilis Using Cardiolipin Antigen: Preliminary Report, *J. Ven. Dis. Inform.* **27**:169 (July) 1946.

Shaffer ³⁶ reports that among a group of 150 military separatees with no history of syphilis or antisyphilitic therapy and with no evidences of syphilis other than positive reactions to serologic tests at the time of separation from the armed services 43 per cent definitely proved not to have syphilis, 40 per cent continued to show conflicting serologic results and in only 17 per cent could a definitive diagnosis of syphilis be made! He recommends that a more conservative attitude be followed in the serologic diagnosis of latent syphilis when no history of the disease exists.

TABLE 1.—*Progress Report on the Cooperative Separatee Referral and Case-Finding Program of the Army, Navy, Public Health Service and State Health Departments**

Results of Investigation	All Separatees Referred for Diagnosis or Health Department Follow-Up (Reported Through Dec. 31, 1946 with at Least Two Months for Investigation)†			
	Positive or Doubtful Reaction of the Blood No History of Treatment		With History of Treatment	
	Number	Per Cent	Number	Per Cent
Total reported	108,960	100.0	85,724	100.0
No disposition received.....	19,891	18.3	14,337	16.7
Not examined ‡	26,146	24.0	19,207	22.4
Total examined	62,923	57.7	52,180	60.9
Not infected and no treatment necessary...	41,755	66.4	36,155	69.3
Under treatment prior to investigation....	4,601	7.3	6,359	12.2
Syphilis brought to treatment.....	16,567	26.3	9,666	18.5
Primary.....	560	0.9	305	0.6
Secondary.....	1,219	1.9	203	0.4
Early latent.....	7,856	12.5	3,041	5.8
Neurosyphilis.....	341	0.5	167	0.3
Other stage.....	2,422	3.9	2,112	4.1
Unknown stage.....	4,169	6.6	3,833	7.3

* Source: separatee tabulations prepared by state and regional tabulating units.

† Report on Mississippi residents through December 1945 and on California, Florida, Kentucky, Louisiana and New York city residents through June 1946.

‡ Unable to locate, moved out of area, uncooperative and similar reasons.

The experience of Rosenthal and Sobel ³⁷ is similar. Among 508 members of the armed forces with no history of syphilis who were referred to the Department of Health in New York city because of positive or doubtful reaction to the serologic test for syphilis made at separation, a diagnosis of syphilis was established in only 23 (5 per cent). Four hundred and seventy-seven (94 per cent) of those referred had had nonspecific reactions to serologic tests and were thought not to have syphilis. The diagnosis was pending in 8 persons in the group at the time of this report.

36. Shaffer, L. W.: Nonspecific Serologic Tests for Syphilis, *Am. J. Syph., Gonorr. & Ven. Dis.* **31**:221 (March) 1947.

37. Rosenthal, T., and Sobel, N.: Syphilis in Army Separatees, *New York State J. Med.* **46**:2042 (Sept. 15) 1946.

tests with the complement saturation method and repeated Wassermann tests on fresh serum and Kahn flocculation tests.

Serum Preservation.—Merthiolate (sodium ethylmercurithiosalicylate) is an effective preservative and decontaminant for serum specimens intended for shipment over considerable distances. The recommended concentration (1 mg. of merthiolate per cubic centimeter of serum) has been shown not to produce nonspecific reactions in sterile serums. Recently some have questioned whether the addition of merthiolate causes a decrease in serologic titer in syphilitic serums. Rein and Bossak,²⁸ who have studied this problem, report that the reduction in serologic titer noted in stored, merthiolated serum is due to the temperatures to which the specimens are subjected rather than to any deleterious effect of merthiolate.

Croft and Smith²⁹ have studied twenty bactericidal agents as preservatives for syphilitic reagin. Serum from patients with syphilis and from normal persons was tested by the Kahn procedure at various intervals over periods of two and one-half to four weeks, the specimens having been stored at room temperature. None gave greater preservation than merthiolate, which was efficacious, depending on the amount of original contamination, in concentrations of 1:1,000 and 1:10,000. A method of preserving serum for shipment by mail with merthiolate in a concentration of 1:2,500 is described. Less than 4 per cent of two hundred specimens so preserved showed any significant decrease in titer after one week, and only 7.3 per cent deteriorated significantly in three weeks. Test specificity was not affected when concentrations of merthiolate of less than 1:1,000 were used.

FALSE POSITIVE REACTIONS TO SEROLOGIC TESTS

The problem of false positive reactions to serologic tests for syphilis, brought more and more into focus because of increasingly widespread routine use of serodiagnostic tests (especially during and since World War II, when millions of serologic tests have been performed on inductees, separatees and prospective blood donors), is a serious and vexing one. The year has seen growing discontent because of the lack of specificity inherent in the sensitive serologic tests in current use.

In general, the more sensitive the serodiagnostic test, the less specific it is. Indeed, Kahn³⁰ has recently rediscovered a phenomenon well

28. Rein, C. R., and Bossak, H. N.: Merthiolate (Sodium Ethyl Mercuri Thiosalicylate) as a Preservative in Sera for the Serodiagnosis of Syphilis, *Am. J. Syph., Gonorr. & Ven. Dis.* **30**:343 (July) 1946.

29. Croft, C. C., and Smith, L. L.: Preservatives for Syphilitic Serum with Special Reference to the Use of Merthiolate, *J. Lab. & Clin. Med.* **31**:1101 (Oct.) 1946.

30. Kahn, R. L.: Universal Serologic Reactivity with Lipid Antigens: Basis for "False Positives," *Am. J. Pub. Health* **37**:283 (March) 1947.

The causes of this general dissatisfaction, in which the reviewers share, seem both social, technical and biologic. Unquestionably the social procedure of mass blood testing has emphasized, though it has not created, the problem. From the technical standpoint, the effort of serologists over four decades to increase sensitivity has exceeded the "optimum range" (of sensitivity versus specificity) to a point at which most if not all current serologic technics are too sensitive. Many of the supposed "biologic false positive" results are indubitably due to technical error. Finally, World War II has exposed an adult population to many extraneous factors known to produce biologic false positive results—factors which usually occur in infants or children (who are not subjected to routine serologic testing), such as vaccinia and acute exanthems, or which normally are rare in the United States, such as tropical diseases.

To the reviewers it is strongly suggested that all present day serologic technics, based as they are on a nonspecific phenomenon which itself is not understood, are unsatisfactory diagnostic weapons. There is needed fundamental biologic and immunochemical research probably based on the successful, but not yet accomplished, growth of *T. pallidum* on artificial mediums, a by-product of which may well be the development of wholly new serologic technics and the abandonment of the current serologic cookbookery and empiricism.

Biologic False Positive Serologic Reactions: Malaria.—In a controlled study of sporozoite-induced vivax malaria, Rein and Kent⁴² examined a series of 7,493 serum specimens obtained at varying intervals from 90 nonsyphilitic volunteers, using a battery of seven serodiagnostic tests for syphilis. In 57 (63.3 per cent) of the 90 infected subjects biologic false positive reactions developed with one or more of the tests during the course of the disease. In the great majority of subjects the nonspecific reaction was transitory and of low degree. Of the battery of tests employed, the highest percentage of false positive reactions was observed with the Kahn standard test and the lowest with the Hinton flocculation test. A microflocculation test with cardiolipin antigen yielded results of exceptional specificity.

Seeking to determine the extent to which malarial serums react with lipid tissue extract antigens under technical conditions favorable for the elicitation of nonsyphilitic reactions, Kahn, Wheeler and Adams⁴³ found that serums of malarial origin showed a greater tendency to precipitation with lipid antigens than those of nonmalarial origin.

42. Rein, C. R., and Kent, J. F.: False Positive Tests for Syphilis: A Study of Their Incidence in Sporozoite-Induced Vivax Malaria, *J. A. M. A.* **133**:1001 (April 5) 1947.

43. Kahn, R. L.; Wheeler, A. H., and Adams, C.: Studies on Serology of Malaria: III. Malarial Precipitation Reactions with Lipid Antigens, *J. Nat. Malaria Soc.* **6**:74 (March) 1947.

questionable authenticity, 13 per cent had nonsyphilitic persistently positive reactions, 7 per cent had congenital syphilis and 40 per cent had acquired syphilis. The rates for false positive reactions and the incidence of congenital syphilis were essentially constant with all age groups. The incidence of acquired syphilis progressively increased with advance in years. In this author's experience the finding of a positive or doubtful reaction to the serologic test led to a diagnosis of syphilis in 47 per cent of a group of healthy American men. Weakly positive reactions proved to mean the presence of syphilis in only 20 per cent of the group, whereas strongly positive reactions proved to mean syphilis in 80 per cent of the group.

The statistics of the Selective Service on more than fifteen million registrants reveal that approximately 5 per cent of men of military age had some form of venereal disease at the time of their physical examinations. The estimated incidence for white registrants was 2 per cent, while the incidence among Negroes was 22 per cent. Among Negroes venereal disease was the second most frequent cause for rejection.

Greve's analysis³⁵ of Selective Service data shows that:

1. The majority of rejections for syphilis were made on the basis of a positive serological blood test alone.
2. Syphilis was the principal cause for the rejection of 271,000, or 6.0 per cent, of those registrants in rejected classes on January 1, 1945. As of the same date there were 18,400 registrants, or 0.4 per cent of all rejected registrants, who had been rejected for gonorrhea and venereal diseases other than syphilis.
3. Approximately 5 per cent of the registrants were found to have a venereal disease at the time of physical examination.
4. The rejection rate for syphilis decreased from 24 per 1,000 examined in peacetime to 4 per 1,000 examined in 1944. The rejection rates for gonorrhea and other venereal diseases decreased from 7 to 0.3 per 1,000 registrants examined during this same period.
5. The decrease in the rejection rate was the result of changes in standards of acceptance which ultimately provided for the acceptance of registrants with all except complicated forms of venereal diseases.
6. Venereal diseases are reported more frequently among Negroes than among white registrants, and rejection rates also are consistently higher among Negro registrants.
7. The prevalence of syphilis increases with advancing age, although the ratio between the white and Negro prevalence rates decreases from a Negro rate which is 19 times the white rate in the age group 21-25 years to about 9 times the white rate among registrants 31-35 years of age.
8. Among white registrants gainfully employed, the percentage of rejections for syphilis was highest among "other service workers" and lowest among farmers and farm laborers and students, while among Negroes it was highest among domestic and protective service workers and lowest among farmers, farm managers and farm laborers.

35. Greve, C. H.: Venereal Diseases Found in Selective Service Registrants, *Am. J. Pub. Health* **36**:751 (July) 1946.

apparent cause other than blood donation and spontaneous reversal to seronegativity. Barnard may be entirely correct in his contention, but he has not proved it statistically.

Lupus Erythematosus.—White⁴⁹ reports the case histories of 3 patients with lupus erythematosus who despite the absence of evidences of syphilitic infection had presumably false positive reactions to serologic tests for the disease.

Brucellosis.—In the differentiation of false positive serologic reactions from those truly syphilitic, one of the most important considerations is the persistence of the positive reaction. In the majority of cases falsely positive reactions revert to negativity within a few months. Gossels⁵⁰ notes, however, that in recurrent brucellosis positive or equivocal reactions to serologic tests may occur persistently or recurrently over a period of years in the absence of syphilitic infection.

Battle Casualties.—In a study of serologic tests for syphilis performed on soldiers admitted to an evacuation hospital in France, Talmage, Dunn and Breazeale⁵¹ report that 35 per cent of 692 persons wounded in battle had positive or doubtful reactions to serologic tests for syphilis. The highest incidence of such reactions occurred in soldiers whose wounds involved fractures and/or amputations.

Pregnancy.—In a monograph detailing the results of an extensive study of blood serologic reactions for syphilis in pregnant women Penttinen⁵² concludes that pregnancy does not affect the reliability of these tests. He notes that both laboratory errors and biologic false positive reactions occur when tests are made of pregnant women, but in his experience they occur no more frequently than among other groups. Biologic false positive reactions in pregnancy occurred notably with low titers; of the strongly positive reactions, 98.8 per cent occurred in patients with syphilis. A comparison of the distribution of patients with syphilis and patients with false positive reactions in relation to the first and the latter half of pregnancy brought forth nothing to support the conjecture that the duration of pregnancy might influence the results of serologic tests for syphilis.

Injections of Penicillin.—Reassuring indeed in these days of false positive reactions to serologic tests for syphilis accompanying such

49. White, C. J.: The Problem of Positive Serologic Tests for Syphilis in Lupus Erythematosus, *Am. J. Syph., Gonorr. & Ven. Dis.* **31**:235 (March) 1947.

50. Gossels, C. L.: Persistently Seropositive Reaction for Syphilis in Chronic Brucellosis, *Virginia M. Monthly* **74**:82 (Feb.) 1947.

51. Talmage, W. R.; Dunn, C. W., and Breazeale, E. L.: Effect of Battle Casualties on Serodiagnostic Tests for Syphilis, *Bull. U. S. Army M. Dept.* **6**:741 (Dec.) 1946.

52. Penttinen, K.: On the Wassermann and Kahn Reactions During Pregnancy, Helsinki, Mercatorin Kirjapaino, 1946.

It should be pointed out that the over-all experience with mass serologic testing of separatees has not been as unfortunate as these authors suggest. The United States Public Health Service has recently made available the data as reported throughout the nation (table 1).

Asking the question "Is mass serology (sic) worth while?" Pilcher³⁸ protests vigorously against what he calls the "ritualistic orgy of blood-letting" of mass serologic testing. He summarizes the results of ten years of openly fighting syphilis, with serologic tests as the leading method of campaigning, as follows:

1. Public health agencies have received a great deal of publicity.
2. Public health agencies have been greatly expanded.
3. The general public has been informed and grossly misinformed about syphilis.
4. The incidence of syphilis has been decreased by a comparatively small margin.
5. An untold amount of the taxpayers' money has been spent.³⁹

Among the many who have recently become increasingly concerned over the nonspecificity of current serodiagnostic tests for syphilis, none is more bitter than Barnard.⁴⁰ This author is emphatically opposed to mass blood tests as being "medically unsound, economically wasteful and socially harmful." He states further that "as a result of certain misconceptions on the import of the serologic tests many thousands of individuals have been subjected to needless treatment, indignity and mental suffering; homes have been disrupted and lives wrecked."

Porter⁴¹ is appalled by the estimate that "in the United States there are thousands of nonsyphilitics being treated for syphilis" in view of the facts that treatment is expensive and not without danger and requires a considerable length of time to be carried out adequately. He considers the mental reactions of the patient to be of importance also—"the heartaches, shame, worries and tendency to withdraw from his usual associates." In addition to the well known causes of false positive reactions, this author has encountered "nonspecific reactions" in infections of the upper respiratory tract ("anything from a slight cold to lobar pneumonia"), pregnancy, injuries and burns in which there is destruction of tissue and "most anything that will cause a fever and for no apparent reason at all."

38. Pilcher, J. F.: Is Mass Serology Worth While? *Texas State J. Med.* **47**:540 (Jan.) 1947.

39. The last two of these statements are inaccurate. The incidence of syphilis has probably actually increased in the United States since 1941, though the exact extent is not definitely known. The money spent in venereal disease control is not an "untold amount" but is instead readily measurable at about twenty millions of dollars per year (average over a ten year period).

40. Barnard, R. D.: Are Mass Presumptive Serologic Surveys Justified by the Present Statuses of Serodiagnostic Tests and of Syphilis? *Ohio State M. J.* **43**:249 (March) 1947.

41. Porter, J. R.: The Positive Serological Reaction Is Not a Diagnosis of Syphilis, *Illinois M. J.* **91**:71 (Feb.) 1947.

average component composition* of the biologic false positive serums with that of normal serums showed no significant differences. No evidence of characteristic qualitative abnormalities was observed either in syphilitic serums or in biologic false positive serums, nor could the changes in syphilitic serum be related to the serologic activity of the specimens. The authors conclude that they found by means of electrophoretic analysis no basis either for the diagnosis of syphilis or for the differentiation between individual syphilitic and biologic false positive serums.

On the basis of a small series of cases Becker⁵⁶ expresses his belief that the Kahn "verification" test may be used as an adjunct to other procedures in the evaluation of questionable serologic results, although he recommends its use only for qualified syphilologists. The use of cardiolipin-lecithin antigens and of tests performed by the Neurath technic is thought "to be of even greater assistance in identification of nonspecific positive blood tests."

Repeated tests of the blood of normal and of syphilitic rabbits, in which standard serologic technics (Kolmer, Kahn and Kline) as well as the differential temperature "verification" test of Kahn were used, led Sherwood and Collins⁵⁷ to conclude that all normal rabbits have detectable amounts of reagin on one or more occasions when the tests are made repeatedly over a period of weeks. The reagin content of normal rabbits was consistently low and in only 1 animal reached as much as 8 Kahn units. Of 52 rabbits infected with syphilis and tested by Kahn's "differential temperature" technic, only 6 consistently showed the "syphilitic type" of reagin, 2 showed the "biologic type" consistently throughout the period of infection and the remaining 44 showed one or more combinations of the normal biologic, syphilitic and inconclusive types. These results seem to indicate that Kahn's differential temperature "verification" test reveals no qualitative difference between the reagin of normal animals and that of syphilitic animals but does indicate fluctuation in nonspecific factors involved in precipitation of the antigen-reagin complex.

The studies of Lubitz⁵⁸ suggest that whereas in the serum of patients with syphilis the reagin titer is unaffected by continued storage in the refrigerator the titer decreases rapidly in certain serums with false positive reactions. In this study there was no correlation between loss of titer and the initial degree of positivity. The author suggests,

56. Becker, S. W.: Practical Aspects of Verification Tests for Syphilis in Office Practice, *Am. J. Syph., Gonorr. & Ven. Dis.* **31**:225 (March) 1947.

57. Sherwood, N. P., and Collins, C.: Experimental Syphilis: Qualitative and Quantitative Studies of Reagin in Normal and Syphilitic Rabbits, *Am. J. Syph., Gonorr. & Ven. Dis.* **30**:571 (Nov.) 1946.

58. Lubitz, J. M.: False Positive Kahn Reactions: Loss of Titer on Storage of Serum in Ice Box, *Am. J. Clin. Path.* **16**:768 (Dec.) 1946.

Vaccinia.—Tey and Tello ⁴⁴ have studied the serologic reactions of 40 subjects following vaccination for smallpox. Of these, 29 were known to be nonsyphilitic, and 11 had been treated for syphilis to the point of seronegativity. Of those without syphilis, transient positive serologic reactions developed in 33 per cent, all of which were of the "general biologic" type with Kahn's "verification" test. Of the 11 known to have had syphilis, positive reactions developed in 4; one was of the "general biologic" type, two were of the syphilitic type and one was inconclusive.

Blood Donation.—During World War II, the experiences of several American Red Cross blood donor centers suggested the possibility that blood donation occasionally is a factor in the production of positive serologic reactions in nonsyphilitic donors. Three publications of significant worth on this subject were discussed in last year's review.⁴⁵ Barnard ⁴⁶ has examined the data set forth in these three publications, making certain statistical adjustments to make the three series of patients comparable. His reevaluation of the data of Boynton ⁴⁶ and of Boerner, Nemser and Stokes ⁴⁷ adds weight to the earlier contention of himself and his co-workers ⁴⁸ that transiently false positive reactions to serologic tests for syphilis may result from phlebotomy. There is a sharp drop in the rate of seropositivity after the first blood donation, which is due to elimination of donors who initially had strongly positive reactions. There then appears to be a secondary rise in the seropositivity rate after the second donation. After this secondary rise, there is a gradual fall to zero as the number of phlebotomies per donor is increased because of the continued weeding out of "serologic reactors."

Despite these statistical contrivances there remains the possibility that the apparent increase in seropositivity rates may have been due to chance alone, as the usual significant tests for comparing percentages show no statistically valid differences. Of greater significance remains the fact that a few persons have been observed who demonstrated the sequence of initial seronegativity, confirmed seropositivity with no

44. Tey, J. A., and Tello, E. E.: Vacunación antivariólica y serorreacciones, Rev. Univ. nac. Córdoba **33**:3, 1946.

45. Barnard, R. D.: An Examination of Some Data on the Relationship of Blood Donation to False Positive Serologic Tests for Syphilis, Urol. & Cutan. Rev. **50**:406 (July) 1946.

46. Boynton, M. H.: The Incidence of Positive Serologic Reactions in Multiple Blood Donors, Am. J. Syph., Gonorr. & Ven. Dis. **30**:252 (May) 1946.

47. Boerner, F.; Nemser, S., and Stokes, J. H.: A Study of the Effect of Bleeding and of Repeated Blood Donation on Serologic Tests for Syphilis, Am. J. M. Sc. **211**:571 (May) 1946.

48. Barnard, R. D.; Rein, C. R. and Doan, C. A.: False Positive Serologic Tests for Syphilis Following Blood Donation, Am. J. Syph., Gonorr. & Ven. Dis. **30**:255 (May) 1946.

genital. There were multiple chancres in 12 per cent of the patients studied. Lesions in the coronal sulcus were most frequently firmly indurated whereas those on the shaft of the penis were least frequently. Preputial edema was noted in 7 per cent of the patients.

The frequency of occurrence of syphilitic lesions of the cervix uteri has long been known to be in proportion to the diligence with which they are sought. Guerriero, Mantooth and Moore⁶² report that identification of *T. pallidum* by dark field examination was possible in 27 women with primary lesions of the cervix and in 14 with secondary manifestations of syphilis. For only 1 patient was a diagnosis of late syphilis established and this by biopsy rather than by visualization of the causative organism. Of significance is their observation that 90 per cent of patients with early syphilitic lesions of the cervix had other complaints such as malaise, fever, arthralgia, anorexia, serosanguineous leukorrhea or contact vaginal bleeding.

Rattner⁶³ reminds physicians that syphilis and scabies may occur together and that because of its inflammatory nature and unpleasant subjective symptoms scabies may obscure a coincident syphilitic infection. It is urged that caution be exercised lest lesions thought to be scabetic be dismissed as such without follow-up observations to rule out a concomitant infection with syphilis.

Secondary Manifestations: Epitrochlear Lymphadenopathy.—The epitrochlear lymph nodes are seldom palpated routinely; most often they are sought when their enlargement is expected. This practice has tended to establish the belief that all palpable epitrochlear nodes are abnormal, because their normal size and frequency of palpability are not generally appreciated. There is, in particular, a common belief that enlargement of the epitrochlear nodes is suggestive of secondary syphilis. Martin,⁶⁴ who has sought to palpate routinely the epitrochlear nodes of 200 soldiers and 100 male civilians, found that these nodes are palpable in about 40 per cent of normal persons. Among the group with palpable nodes, in 14 per cent they exceeded the size of a cherry stone. There was no evidence to support the belief that epitrochlear lymphadenopathy was more characteristic of syphilis than of other diseases.

Tonsillar Lesions.—Cohen⁶⁵ points out that the pharyngeal lesions of secondary syphilis usually are nondescript and similar to those of Vincent's infection but that syphilis should be suspected when there

62. Guerriero, W. F.; Mantooth, W. B., and Moore, W.: Syphilis of the Cervix, *South. M. J.* **40**:261 (March) 1947.

63. Rattner, H.: Syphilis Masked by Scabies, *J. A. M. A.* **131**:1241 (Aug. 10) 1946.

64. Martin, L.: Palpable Epitrochlear Glands: Incidence of Relation to Syphilis, *Lancet* **1**:363 (March 22) 1947.

65. Cohen, B. M.: Secondary Syphilis of the Tonsils, *U. S. Nav. M. Bull.* **46**:1278 (Aug.) 1946.

trivial incidents as infections of the upper respiratory tract and the donation of blood is the report of Turner.⁵³ This author found no evidence that the addition of penicillin to serum from normal persons provoked false positive reactions, and he states the belief that the therapeutic use of penicillin can be discounted as a source of biologic false positive reactions.

Clinical Approach to Serologic Tests of Questionable Significance.—Callaway⁵⁴ has outlined the approach to questionable serologic results and includes the following requisites: (1) a careful history and physical examination; (2) repeated quantitative serologic tests; (3) repeated serologic tests in different laboratories; (4) complete studies of the blood (white blood cell count, differential studies, smears for malaria and heterophil agglutinations); (5) verification test (Neurath test "or other similar verification test"); (6) "family and contact" epidemiologic survey; (7) examination of the spinal fluid; (8) fluoroscopy of the heart and aorta, and (9) continued quantitative serologic tests to determine whether the titer is rising or falling.

"Verification" Technics.—In an attempt to devise or perfect methods for the differentiation of true syphilitic serums from biologic false positive serums, there has been at Duke University a systematic investigation of the character and properties of blood serum and serum constituents, reagin and other possible materials involved in serologic reactions. One part of this work was concerned with the electrophoretic analysis of whole serum in order (a) to determine the electrophoretic character of syphilitic human serum, (b) to seek possible characteristic differences between normal, syphilitic and biologic false positive human serums and (c) to provide data for relating the constitution of serum fractions to that of whole serum.

Cooper, Craig and Beard⁵⁵ made electrophoretic analyses on thirteen normal, twenty-eight syphilitic and thirty-two presumably biologic false positive human serums. They report finding significant differences between the average electrophoretic characteristics of syphilitic serums and those of serums from normal persons. These differences consisted in the presence in syphilitic serums of abnormally large relative and absolute amounts of alpha¹ and gamma globulins and proportionately small amounts of albumin. The quantities of alpha² and beta globulins in syphilitic serums were likewise slightly larger than those in normal serums, but the differences were not significant. Comparison of the

53. Turner, R. D.: Nonproduction by Penicillin of False Positive Reactions in Kahn and Kolmer Tests, *Am. J. Clin. Path.* **17**:469 (June) 1947.

54. Callaway, J. L.: The Problem of Doubtful Serologic Tests for Syphilis, *South. Med. & Surg.* **109**:42 (Feb.) 1947.

55. Cooper, G. R.; Craig, H. W., and Beard, J. W.: Electrophoretic Analysis of Syphilitic, Biologic False Positive, and Normal Human Sera, *Am. J. Syph., Gonorr. & Ven. Dis.* **30**:555 (Nov.) 1946.

in syphilis, reports on 5 patients who were, in his opinion, reinfected and on 1 patient thought to have sustained a superinfection. All the patients had been treated with arsenicals and bismuth.

Discussing the question of "cure" of syphilis, Bohnstedt⁷⁰ reports 21 cases of reinfection with syphilis after therapy with arsphenamine and bismuth. His criteria for reinfection are: (1) the diagnosis of both the first and the second infection must be proved by dark field examination and serologic evidence; (2) the first infection must have been "adequately" treated and seronegativity attained; (3) the second infection must be manifested by a primary lesion. In the presence of secondary manifestations the differentiation between relapse and reinfection cannot be made; (4) the location of the second chancre must be different from that in the first infection, and (5) the possibility of a second exposure to a sexual partner with infectious lesions must be demonstrated.

Musing over the problem of relapse versus reinfection, Leider⁷¹ concludes that syphilis of the prearsenotherapy era could not have been attended with reinfection, since even if symptomatic or bacteriologic cure occurred only superinfection and reactivation of the disease process were possible because of the immunoallergic state. Syphilis of the era of traditional arsenotherapy rarely was attended with reinfection. The determination of the fact of reinfection could seldom be made because of its similarity to the commoner phenomena of relapse, superinfection and reactivation of the disease process. Syphilis of the present and of the near future is, and will be, characterized by more frequent reinfection. The prospects of more frequent reinfections will significantly influence the technics of venereal disease control.

Latent Syphilis.—Jordon and Dolce⁷² present data obtained on 169 patients with latent syphilis observed for ten years or more. The patients were divided into two groups on the basis of the total amount of treatment received. Group I, those "poorly treated," consisted of 69 patients who received either no treatment or less than forty injections, and group II, considered "well treated," consisted of 100 patients who received forty or more injections of an arsenical and a heavy metal either alone or in combination.

Between 20 and 25 per cent of those "poorly treated" had some late complication, most often cardiovascular involvement. The incidence

70. Bohnstedt, R. M.: Reinfektion bei Syphilis, Ztschr. f. Haut- u. Geschlechtskr. 11:325 (June) 1947.

71. Leider, M.: Semantic Confusion and Resolution in the Concepts of Cure in Syphilis and of Reinfection with Syphilis, Am. J. Syph., Gonorr. & Ven. Dis. 30:344 (July) 1946.

72. Jordon, J. W., and Dolce, F. A.: Latent Syphilis: Study of One Hundred and Sixty-Nine Cases Observed Ten Years or More, Arch. Dermat. & Syph. 54:1 (July) 1946.

by way of explanation of his findings; that either the nonspecific reagin is more labile and deteriorates on standing or an inhibitor present in serum may become activated.

Other Serologic Procedures in Syphilis.—The Weltmann serum coagulation test, like the erythrocyte sedimentation test, the cephalin flocculation test and the formol-gel test, is an empiric nonspecific test used as a laboratory aid in the diagnosis of disease and in the following of its clinical course.

With respect to syphilis, the reports in the literature concerning the Weltmann serum coagulation test are conflicting. Callaway,⁵⁹ who has studied the reaction in 610 patients with syphilis, found a mild prolongation of the coagulation band in all forms of syphilis with the exception of congenital syphilis. Thirty-two patients with early syphilis received six months' treatment with metal chemotherapy, without any appreciable change in the results of the test. Neither fever therapy nor the use of penicillin altered the coagulation band of patients with neurosyphilis. There was no apparent correlation between the Weltmann reaction and the positivity or negativity of either the blood or the cerebrospinal fluid.

A novel approach to the serodiagnosis of syphilis is that proposed by Bergamasco.⁶⁰ This investigator reports that in the presence of Kahn antigen the erythrocyte sedimentation rate of patients with syphilis is significantly accelerated. He has found a fairly close correlation between the reaction in tests of this type and the Wassermann reaction. "Nonspecific" positive accelerated sedimentation rates were observed in 2 patients, 1 of whom had sarcoid and the other acute rheumatic fever.

CLINICAL MANIFESTATIONS

Early Syphilis: Primary Lesions.—From data gathered in Java before and after World War II, Simons⁶¹ has derived certain observations on the clinical features of the primary lesion of syphilis. In 680 male patients with early syphilis this observer found the primary lesion on the glans penis in approximately half of the cases (coronal sulcus, 25 per cent; frenulum, 12.5 per cent; meatal or parameatal region, 10 per cent, and other portions of the glans, 2.5 per cent). Twenty-five per cent of chancres were on the prepuce, slightly more often on the inner surface than on the outer, 15 per cent were on the penile shaft and 10 per cent were paragenital (scrotum, pubis and thighs) or extra-

59. Callaway, J. L., and Adams, L. W.: The Weltmann Serum Coagulation Reaction in Syphilis, *Am. J. Syph., Gonorr. & Ven. Dis.* **31**:216 (March) 1947.

60. Bergamasco, A.: La velocità di sedimentazione della emazia come indice di reazioni specifiche nella sifilide, *Arch. ital. dermat., sif. e vener.* **19**:83, 1946.

61. Simons, R. D. G. P.: Clinical Features of Over 1,200 Syphilitic Chancres and Chancroids and Over One Hundred and Forty Cases of Lymphopathia Venerea, *Acta dermat.-venereol.* **27**:115, 1946.

ing to the clinical records of 28 cases that were available for analysis, the lesion occurred in 23 men and in 5 women; 24 patients were white and 4 were Negroes, and the average age was 38.5 years. A clinical diagnosis of hepatic syphilis had been made in only 3 cases. In 18 cases the liver was palpable; in 6 instances it was nodular, and in 10 tenderness was present. The spleen was palpable in 13 cases. Jaundice occurred in 8 cases, ascites in 18, hematemesis in 7 and irregular fever in 12. The authors stress the paucity of symptoms and the relative frequency of physical signs.

Syphilis of the Lung.—Involvement of the lung is a rare manifestation of acquired syphilis, and there is considerable difference of opinion regarding its diagnosis and incidence. The controversy is attributable to the relative nonspecific clinical features, to the variation in diagnostic criteria employed and to the fact that the true nature of the lesion may be overlooked because of its obscure nature and the presence of secondary infection.

Wilson,⁷⁶ who has recently reviewed the subject of pulmonary syphilis, states that the clinical and roentgenologic manifestations of syphilis of the lung are those of any chronic pulmonary infection and most often simulate the manifestations of pulmonary tuberculosis. This author, in reporting a case with the postmortem findings, including the demonstration of spirochetes in stained section, states the belief that "the reported incidence of pulmonary syphilis would rise if this diagnosis would be considered more frequently in the presence of chronic progressive pulmonary infection associated with a positive serologic reaction and other stigmas of syphilis." Whether the expected rise in the reported incidence in these circumstances would be justifiable is, in the opinion of the reviewers, another matter.

The clinical, radiologic and pathologic aspects of acquired pulmonary syphilis were discussed by Kulchar and Windholz.⁷⁷ In these authors' expressed opinion the rarity of pulmonary syphilis, its tendency to imitate other diseases and the low index of suspicion among physicians all are factors responsible for the failure to recognize clinically late syphilis of the lung. Four cases of possible late pulmonary syphilis are reported, in none of which the diagnosis was established on more than presumptive evidence.

Paroxysmal Hemoglobinuria.—Paroxysmal cold hemoglobinuria is a phenomenon almost always associated with syphilitic infection. Wag-

76. Wilson, J. M.: Acquired Syphilis of the Lung: Report of a Case with Autopsy Findings and Demonstration of Spirochetes, *Ann. Int. Med.* **25**:134 (July) 1946.

77. Kulchar, G. V., and Windholz, F.: The Clinical, Radiologic and Pathologic Aspects of Late Pulmonary Syphilis: Effects of Penicillin Therapy, *Am. J. Syph., Gonorr. & Ven. Dis.* **31**:166 (March) 1947.

are bilateral, irregular and superficial denudations or ulcerations over the surfaces of the tonsils or pharynx or a thin, nonodororous, bluish white translucent membrane.

Infectiousness of Cervical Secretions.—Tello and Baggio⁶⁶ were unable to demonstrate the treponemes of syphilis in the cervical secretions of 2 women with primary syphilis or in those of 13 women with secondary manifestations in the absence of clinical lesions of the cervix.

Early Syphilitic Nephropathies.—Thomas and Schur⁶⁷ report their experiences with syphilitic nephropathies, reviewing the patients with secondary syphilis treated in the wards of the Bellevue Hospital since 1940. Twelve, or less than 0.3 per cent of those treated for secondary syphilis, had markedly abnormal urinary symptoms, which responded promptly to antisyphilitic therapy. Of the 12 cases of renal involvement, 10 were classified as cases of syphilitic nephrosis and 2 as cases of nephritis, although the authors were unable to draw any distinct line between the two conditions in some instances. In syphilitic nephrosis, results of tests of renal function usually were not significantly abnormal, but pronounced albuminuria and cylindruria were present. In early syphilitic nephritis there occurred less albuminuria and more hematuria. In 1 case of diffuse glomerulonephritis apparently due to secondary syphilis, in which there were hypertension and secondary anemia, there was response to antisyphilitic therapy with penicillin. Early syphilitic nephropathies have no demonstrable sequelae.

The possibility that subclinical involvement of the kidney may exist in early syphilis and that a focal Herxheimer reaction affecting a subclinically involved renal parenchyma may produce acute syphilitic nephrosis is suggested by Scott and Clark.⁶⁸ They have observed a patient with secondary syphilis in whom the pretreatment urinalysis had revealed nothing abnormal and in whom there developed, after penicillin therapy, the classic evidences of the nephrotic syndrome, all of which subsided spontaneously and promptly without further antisyphilitic treatment. The patient's therapy had been accompanied with a severe febrile Herxheimer reaction.

Reinfection and Relapse.—Peli,⁶⁹ after summarizing some of the European literature on the question of reinfection and superinfection

66. Tello, E. E., and Baggio, P. A.: Sifilis: La contagiosidad de las secreciones cervicales en las sifilíticas floridas, Rev. Univ. nac. Córdoba **33**:657 (May-June) 1946.

67. Thomas, E. W., and Schur, M.: Clinical Nephropathies in Early Syphilis, Arch. Int. Med. **78**:679 (Dec.) 1946.

68. Scott, V., and Clark, E. G.: Syphilitic Nephrosis as a Manifestation of a Renal Herxheimer Reaction Following Penicillin Therapy for Early Syphilis, Am. J. Syph., Gonorr. & Ven. Dis. **30**:463 (Sept.) 1946.

69. Peli, G.: Reinfessione e superinfessione sifilitica, Arch. ital. dermat., sif. e vener. **19**:290, 1946.

on approximately 600 patients studied over a period of years at the Brooklyn Hospital. Patients with hypertension, rheumatic fever, hyperthyroidism and unexplained cardiac enlargement were excluded. Their criteria for the diagnosis of uncomplicated syphilitic aortitis were: (1) the patient must have had syphilis beyond a reasonable doubt; (2) there must be no evidence of any other disease that might dilate the aorta; (3) the patient must be 40 years of age or younger; (4) there must be roentgenographic or fluoroscopic evidence of aortic dilatation; (5) there may be a hollow, accentuated aortic second sound, and (6) there may be a systolic murmur at the aortic area. The validity of these criteria was tested by a comparison of the clinical diagnosis with the observations at autopsy and by an analysis of the group to discover in how many patients more advanced lesions of cardiovascular syphilis developed.

Cardiovascular syphilis developed five times as often among patients receiving no treatment or practically none as among those to whom "adequate" courses of metal chemotherapy had been given. The incidence of syphilitic heart disease decreased as the amount of antisyphilitic therapy increased. When treatment was administered for six or more years after the appearance of the chancre evidence of cardiac involvement developed four times as often as when the treatment was completed within three years from the onset of the disease. Aortic regurgitation and aneurysm appeared much more frequently among those who had received little or no antisyphilitic therapy.

Aneurysm.—The clinical and roentgenologic features of aneurysm of the descending thoracic aorta are discussed by Lowenberg and Baer.⁸³ These authors mention the gastrointestinal syndromes produced by this lesion and emphasize the anatomic relationship of the aorta to the esophagus, which may be displaced by aneurysms in this location. Deviation of the esophagus anteriorly and to the left occurs with aneurysms at the diaphragmatic hiatus. The only other lesion commonly producing this picture is a congenital anomaly—the right-sided aortic arch. Erosion of the lower thoracic vertebrae is considered to be another characteristic sign of aneurysm of the lower thoracic aorta.

Lang⁸⁴ discusses the value of roentgenography in the diagnosis of abdominal aortic aneurysm. Calcification within the aneurysmal wall he believes to be more frequent in arteriosclerotic than in syphilitic aneurysms. A pathognomonic roentgenographic sign is pressure erosion of the vertebral bodies, which tend to assume a scalloped appearance

83. Lowenberg, S. A., and Baer, S.: Aneurysm of the Descending Thoracic Aorta, *Am. Heart J.* **32**:653 (Nov.) 1946.

84. Lang, E. F.: X-Ray in the Diagnosis of Abdominal Aortic Aneurysm, *Harper Hosp. Bull.* **5**:21 (April) 1947.

of progression appeared to be significantly higher among patients whose reactions to the serologic tests remained strongly positive after therapy. There was no evidence that an extensive early tissue reaction improved the ultimate prognosis.

In the group of 100 patients who received more than a total of forty injections of antisyphilitic drugs complications developed in only 4. There appeared to be no relationship between the incidence of complications and the serologic status, and seroresistance did not seem to detract from the prognosis. Arsenical drugs appeared to be more efficacious in the prevention of late complications than heavy metals.

The authors were unable to determine from their studies the optimum amount of antisyphilitic therapy for patients with latent syphilis, but they state the belief that forty or sixty injections are adequate. Since the highest percentage of complications occurred in patients receiving little arsenical therapy and since the outcome appeared to be only slightly influenced by prolonged heavy metal therapy, the authors believe that more emphasis should be placed on the use of arsenical therapy in patients with latent syphilis.

The management and treatment of patients with latent syphilis and of those with late symptomatic syphilis have been discussed in general terms by McElligott.⁷³ This author decries the use of routine schedules of therapy and stresses the fact that the management of patients should be individualized. The objects of treatment should be (1) the healing of lesions and the relief of symptoms if these are present, (2) the prevention of progression or relapse and (3) serologic reversal (least important of all). Stressing the maxim that "syphilis must not be allowed to spoil lives," he notes that although inadequate therapy may do this unnecessarily prolonged treatment may have the same result.

Late Syphilis: Syphilis of the Breast.—Kampmeier⁷⁴ indicates that when syphilitic lesions of the breast are solitary they may readily be confused with other conditions. To illustrate the point, he reports the case history of a 60 year old white woman with a chancre of the nipple and that of a 30 year old Negro woman with a gumma of the breast. Gummatous mastitis is to be differentiated from carcinoma. Most often this differentiation is made pathologically after mastectomy.

Syphilis of the Liver.—Symmers and Spain⁷⁵ report that over a period of thirty years hepar lobatum was encountered one hundred and two times among 23,792 necropsies at Bellevue Hospital. Accord-

73. McElligott, G. L. M.: The Management and Treatment of the Late and Latent Syphilitic, *Brit. J. Ven. Dis.* **22**:171 (Dec.) 1946.

74. Kampmeier, R. H.: Syphilis of the Breast: Chancre and Gumma, *Am. Practitioner* **1**:395 (March) 1947.

75. Symmers, D., and Spain, D. M.: Hepar Lobatum: Clinical Significance of the Anatomic Changes, *Arch. Path.* **42**:65 (July) 1946.

and have found it concerned largely with the two major interrelated problems of incidence and prognosis. Critically assessing the available studies, these authors found that deficiencies were so numerous that they vitiated almost completely their value as a practical guide to therapy and prognosis in the individual case. These deficiencies fall into one or more of the following categories: insufficient number of cases, insufficient observation period, faulty statistical analysis or failure to take into consideration one or many of the variables concerned. These variables include age, race and sex of the patient, duration of infection at the time of examination of the cerebrospinal fluid, treatment received prior to the first positive reaction of the spinal fluid, degree of positivity of the reaction of the spinal fluid and the type and amount of therapy received after the diagnosis of asymptomatic neurosyphilis has been established.

In another paper Hahn and Clark⁸⁷ sought to determine the prognosis of asymptomatic neurosyphilis, with attempted consideration for the first time of the variables just mentioned. Their clinical material consisted of 533 patients who had at least two examinations of the spinal fluid and 467 patients who had at least two physical examinations. The observation period was less than two years in approximately 40 per cent and more than five years in approximately 35 per cent of the patients.

Race and sex appeared to be of slight importance in the prognosis of asymptomatic neurosyphilis. As to age, the younger the patient and the more recently acquired the syphilitic infection, the more favorable was the prognosis during the first ten years of observation. The more strongly positive the reaction of the spinal fluid on initial examination, the more unfavorable was the final condition of the spinal fluid and the greater was the probability of the development of clinical neurosyphilis. The final outcome in the spinal fluid was significantly better and the probability of the development of clinical neurosyphilis by the tenth year of observation significantly less for patients with early asymptomatic neurosyphilis (duration of syphilis, less than two years) than for patients with late asymptomatic neurosyphilis despite less intensive treatment in the former group.

The longer the period of observation, the greater was the percentage of patients in whom the reaction of the spinal fluid became negative, and the greater also was the probability of the development of clinical neurosyphilis. This seeming paradox is explained on the basis of the fact that the two groups were composed largely of patients who followed divergent paths. Progression of the spinal fluid to positivity was found to be an ominous prognostic sign.

87. Hahn, R. D.; Clark, E. G., and others: Asymptomatic Neurosyphilis: Prognosis, *Am. J. Syph., Gonorr. & Ven. Dis.* **30**:513 (Nov.) 1946.

ley, Zinkham and Siebens⁷⁸ have found evidence that the serum hemolysin is activated by carbon dioxide and inhibited by sulfanilamide and cyanide, two substances which inhibit the activity of carbonic anhydrase. The inhibitory effect was shown to be reversible.

In the case of paroxysmal hemoglobinuria reported by Goldberg⁷⁹ treatment with 3,600,000 units of penicillin did not prevent the occurrence of port wine-colored urine after exposure of the patient to a temperature of 40 F. although some of the constitutional symptoms were at least temporarily ameliorated.

Cardiovascular Syphilis: Isolation of T. Pallidum From the Aorta.—Hu and his fellow workers⁸⁰ have isolated virulent *T. pallidum* from the aorta of a Chinese rickshaw puller who died of syphilitic aortitis with aortic regurgitation. The aortic tissue was inoculated intratesticularly into a rabbit thirty-two hours after the death of the patient. Viable organisms also were isolated from juxta-articular nodules but not from the circulating blood or from the mitral valve. The patient died twenty-five years after acquiring syphilis without ever receiving specific antisyphilitic treatment. This is, as far as the authors could ascertain, the first time that viable pathogenic treponemes have been shown to be present in the walls of the diseased aorta. The fact that virulent *T. pallidum* can be isolated from cadavers several hours after death is of practical importance to the pathologist from the standpoint of possible accidental infection at autopsy.

Diagnosis of Cardiovascular Syphilis.—Lucia and Sears⁸¹ report that in a group of 355 patients observed in a special clinic for the treatment of cardiovascular syphilis the age distribution of the patients examined was such that hypertensive and arteriosclerotic changes made the diagnosis of uncomplicated syphilitic aortitis practically impossible and the diagnosis of syphilitic aortic regurgitation frequently difficult.

Prevention of Cardiovascular Syphilis.—Maynard and Lingg⁸² present additional evidence that the administration of antisyphilitic therapy to patients with early or latent syphilis affords protection against the later development of cardiovascular involvement. Their data are based

78. Wagley, P. F.; Zinkham, W. H., and Siebens, A. A.: A Note on Studies of Hemolysis in Paroxysmal (Cold) Hemoglobinuria, *Am. J. Med.* **2**:342 (April) 1947.

79. Goldberg, L. C.: Treatment of Paroxysmal Hemoglobinuria with Penicillin: Report of a Case, *Am. J. Syph., Gonorr. & Ven. Dis.* **31**:163 (March) 1947.

80. Hu, C. K.; Liu, Y.; Chen, K. C., and Frazier, C. N.: Isolation of Virulent *Treponema Pallidum* from Human Aorta Thirty-Two Hours After Death from Cardiovascular Syphilis, *Am. J. Med.* **1**:301 (Sept.) 1947.

81. Lucia, S. P., and Sears, N. N.: Diagnostic Problems in Luetic Cardiovascular Disease, *California Med.* **65**:207 (Nov.) 1946.

82. Maynard, E. P., Jr., and Lingg, C.: The Prevention of Cardiovascular Syphilis, *Brooklyn Hosp. J.* **4**:18 (July) 1946.

tion of malaria the vertigo disappeared and did not recur. The lack of audiometric and vestibular studies impairs the value of this report.

Primary Optic Atrophy.—McLean⁹⁰ has made follow-up observations on 30 patients treated for syphilitic primary optic atrophy. Neoarsphenamine and bismuth had been given to all the patients; in addition, tryparsamide had been administered to 27, and malaria had been induced in 21. The mean period of observation after treatment was seven and one-half years. On reexamination of the visual fields it was found that in 4 patients the atrophy had improved, in 23 it was unchanged and in 3 it was reduced. Ninety per cent of the patients had maintained their pretreatment visual acuity and visual fields.

Optochiasmatic Arachnoiditis.—Optochiasmatic arachnoiditis may produce a clinical syndrome not unlike that of tumor in the region of the optic chiasm or that of primary optic atrophy. This lesion has not been ascribed to any single cause. Trauma and localized leptomenigitis due to syphilis, mastoiditis, sinusitis, petrositis and chronic rhinopharyngitis have been described as etiologic factors. It has been described as a sequel of trauma, encephalitis and multiple sclerosis and tuberculosis, and it may coexist with Leber's disease and hydatid cyst. In many cases, however, the etiologic factor is not apparent.

Pendergrass and Perryman,⁹¹ who present the case histories of 4 patients with chiasmatic arachnoiditis (1 of whom had syphilis), state the belief that the condition can be diagnosed by pneumoencephalography. They discuss the anatomy of the optic chiasm and certain of its contiguous structures from the standpoint of the roentgenologist. In the pneumoencephalogram it may be possible to demonstrate adhesions, cysts or obliteration of the cisternae in the region of the optic chiasm.

Tabes Dorsalis.—In tabes dorsalis, a study of the vibratory sensation as estimated with the tuning fork is a valuable diagnostic indication of damage to the posterior roots and posterior columns of the spinal cord. Borach⁹² has studied the vibratory sensation quantitatively and has derived a normal curve based on the number of seconds' duration of the vibratory sense at each of eight bony prominences. In the normal person the sensitivity of the upper half of the body to vibration is greater than that of the lower half. Of the factors entering into the interpretation of the test, the author lists the following: 1. Vibratory sensation varies in different persons, some being more sensitive than others. 2. Vibratory sensation tends to diminish with advancing years. 3. For

90. McLean, J. A.: Visual Field Changes in Syphilis of the Central Nervous System, *Canad. M. A. J.* **55**:571 (Dec.) 1946.

91. Pendergrass, E. P., and Perryman, C. R.: Optochiasmatic Arachnoiditis, *Am. J. Roentgenol.* **56**:279 (Sept.) 1946.

92. Borach, J. H.: Test for Quantitative Vibratory Sensation in Diabetes, Pernicious Anemia and Tabes Dorsalis, *Arch. Int. Med.* **79**:602 (June) 1947.

because of greater destruction of the vertebral bodies than of the elastic intervertebral disks, which resist erosion. Because of the anatomic position of the aorta, erosion usually is seen earliest in the left anterolateral position of the body. A more heroic method of diagnosis is by arteriography, with injection of the contrast medium above the lesion following catheterization of the femoral artery. The roentgen appearance after rupture varies with the degree and the site of bleeding. The commonest site of rupture is into the retroperitoneal space, and the roentgenograms show obliteration of details of the psoas muscle on the side of the rupture, with a considerable increase in density as compared to the other side. A similar increase in density with obliteration of the shadow of the psoas muscle occurs with perinephric abscess. Pressure of the hematoma on the structures at the hilus of the kidney may produce hydronephrosis and uremia. Hemorrhage also may occur around an enclosed or fixed portion of the gastrointestinal tract, such as the duodenum, and pressure from the mass of blood may cause obstruction of the intestinal lumen.

The surgical treatment of aneurysms of the abdominal aorta is none too satisfactory, primarily because of the meager collateral circulation which exists. That gradual closure of the aorta, especially at its lower end just above the iliac bifurcation, may be tolerated, however, is evidenced by the goodly number of patients in whom saddle thrombosis develops slowly at the site of atheromatous plaques. The collateral circulation requires the integrity of the iliac arteries.

The defect common to surgical methods producing aortic occlusion from the outside is that with compression there is death of the vessel wall. These degenerative lesions of the aorta, especially in the presence of hypertension, tend to make complete ligature intolerable for any length of time. Possible alternative methods of therapy are the production of gradual fibrosis with nonconstricting applications of cellophane followed later by wiring, complete excision of the sac with transections of the aorta or a combination of proximal banding with partial cellophane wrapping.

DeTakats and Reynolds⁸⁵ have observed a group of 8 patients with aneurysms of the abdominal aorta. Of these, 2 were not subjected to operation, and 2 were merely examined surgically; one aneurysm was wired, and three were banded with cellophane. Among these patients only the 3 treated with cellophane wrapping survived for any length of time.

Neurosyphilis: Asymptomatic Neurosyphilis.—Hahn and Clark⁸⁶ have reviewed the literature concerning asymptomatic neurosyphilis

85. deTakats, G., and Reynolds, J. T.: The Surgical Treatment of Aneurysms of the Abdominal Aorta, *Surgery* **21**:443 (April) 1947.

86. Hahn, R. D., and Clark, E. G.: Asymptomatic Neurosyphilis: A Review of the Literature, *Am. J. Syph., Gonorr. & Ven. Dis.* **30**:305 (July) 1946.

autonomic nervous system is of significance in predisposing the skeletal system to an overreaction to trauma and the development of the Charcot joint.

Bailey and Root⁹⁵ report 17 cases of neuropathic arthropathy of the feet associated with diabetes mellitus. Each patient had destruction of the tarsal and metatarsal bones roentgenologically similar to that observed in Charcot joints. The most striking differences between the true Charcot joint and the diabetic neuropathic foot were the more acute onset of fluid in the joint and swelling of the extremity in the former, the presence of pain in the Charcot joint during the acute stage, the frequent occurrence of new bone formation in the Charcot joint and its rarity in the diabetic neuropathic foot, the occurrence of syphilitic osteosclerosis in areas near the involved joint, the physical evidences of tabes dorsalis in patients with Charcot joints and the relative infrequency of the true Charcot arthropathy in the feet.

Morris⁹⁶ also has observed neuropathic arthropathy of the foot in a patient with diabetes mellitus.

The Treatment of Lightning Pains in Tabes Dorsalis.—Costello⁹⁷ reports a favorable experience with the use of "protamide"⁹⁸ as treatment for tabetic lightning pains. This preparation, a colloidal suspension of processed and denatured proteolytic enzyme (pepsin), was found to be most satisfactorily administered intramuscularly without adjuvants. Injections were given once a week, and a course of twenty injections is recommended. The results of therapy in 89 patients are reported; 42 (47 per cent) are alleged to have obtained complete or almost complete relief of lancinating pains.

Pelner⁹⁹ reports relief of lightning pains and girdle sensations in 2 patients with tabes dorsalis following the intravenous injection of nicotinic acid.

Neurosyphilis in the Tropics.—It is a well known fact that neurosyphilis is rare in the tropics. Some have considered that this is so because of the common occurrence of malaria and other tropical fevers. McCartney,¹⁰⁰ however, notes that syphilis of the central nervous system is rare in the Marshall Islands, where there is no malaria. In this

95. Bailey, C. C., and Root, H. F.: Neuropathic Foot Lesions in Diabetes Mellitus, *New England J. Med.* **236**:397 (March 13) 1947.

96. Morris, M. H.: Charcot's Joint in Diabetes Mellitus, *New York State J. Med.* **47**:1395 (June 15) 1947.

97. Costello, R. T.: A New Treatment for the "Lightning Pains" of Tabes Dorsalis, *Urol. & Cutan. Rev.* **51**:260 (May) 1947.

98. Fuller Laboratories, Inc., 1275 Penobscot Bldg., Detroit.

99. Pelner, L.: The Treatment of Lightning and Girdle Pains in Tabes Dorsalis with Niacin, *New York State J. Med.* **47**:1496 (July 1) 1946.

100. McCartney, J. L.: Why Is Neurosyphilis Uncommon in the Tropics? *Mil. Surgeon* **99**:21 (July) 1946.

A direct comparison of the results of the several types of treatment was not feasible because the supplementary forms of treatment (tryparsamide, malarial therapy) were more frequently given to patients with the more resistant spinal fluids. It was possible, however, to demonstrate in some cases the relatively benign nature of spinal fluid which reacted positively as well as the value of routine chemotherapy in many cases. The incidence of clinical progression over a ten year period in untreated asymptomatic neurosyphilis was estimated at approximately 20 per cent. There was no evidence that the addition of tryparsamide was of value in the treatment of asymptomatic neurosyphilis.

Malarial therapy was given to a relatively small group of patients, over one half of whom had initial "group III" spinal fluids and most of whom had proved resistant to other forms of treatment. The incidence of clinical progression, even in this resistant group, was 9.5 per cent at five years with no further increase at ten years. Spinal fluid progression was not observed, and in 25 per cent of the cases the reaction of the spinal fluid became negative. Fever therapy with induced malaria thus was the most efficacious form of treatment in this type of asymptomatic neurosyphilis.

Anisocoria in Normal Persons.—Meyer⁸⁸ has studied 500 normal subjects with reference to the incidence of anisocoria and of differences of the width of the palpebral fissures. Nearly 17 per cent of the patients showed at least some degree of anisocoria, and in 4 per cent the difference in pupillary size was pronounced. Inequality of the palpebral fissures was even more frequent. Imbalance of sympathetic innervation and differences in refractive errors are considered to be possible explanations for at least some cases of anisocoria, but the author cautions that it should never be dismissed as an unimportant anomaly until a thorough search reveals no other etiologic basis for it.

Vertigo in Neurosyphilis.—Vertigo is rarely the presenting and only symptom of neurosyphilis. That occasionally it may be is evident from a recent report by Alpers.⁸⁹ In his 2 patients the vertigo was paroxysmal, severe and greatly influenced by changes in posture. In 1 patient temporary loss of hearing accompanied the attack of vertigo, but tinnitus was lacking in both cases. In the 2 cases there was a strongly positive reaction of the spinal fluid. It is considered that the vertigo resulted from an interstitial neuritis of the auditory nerve. One patient responded well to therapy with penicillin; the other failed to improve after administration of penicillin, but after therapeutic induc-

88. Meyer, B. C.: Incidence of Anisocoria and Difference in Size of Palpebral Fissures in Five Hundred Normal Subjects, *Arch. Neurol. & Psychiat.* **57**:464 (April) 1947.

89. Alpers, B. J.: Vertigo as the Presenting and Only Symptom of Neurosyphilis, *Am. J. Syph., Gonorr. & Ven. Dis.* **31**:322 (May) 1947.

of syphilis, and in 35 the reactions to serologic tests were negative during their last period of hospitalization.

A comparison of Rosahn's material with that of Bruusgaard¹⁰³ reveals a remarkable similarity. About 39 per cent of the former group of untreated syphilitic patients had postmortem evidences of syphilis, whereas in the latter group 35 per cent had clinical or postmortem lesions. In the Rosahn series 23 per cent died primarily as a result of syphilis, a figure identical with that found by Bruusgaard. Conversely, in the Rosahn series 61 per cent died with no anatomic evidence of syphilis, while Bruusgaard's group included 65 per cent who were without any evidence of organic syphilis. The ratio of positive and negative serologic results in the two groups is somewhat different, but this may be accounted for by (1) the large number of Bruusgaard's patients whose serologic status was not known and (2) probable differences in the sensitivity of the serologic tests employed in the two series.

This study affords further evidence that in a certain proportion of infected persons (17.7 per cent in Rosahn's material) defense mechanisms of the host suffice to effect spontaneous cure of the disease in the absence of treatment of any kind.

The data of Deibert and Bruyere¹⁰⁴ suggest that in the absence of specific treatment patients with syphilis, even though they may escape the crippling late manifestations which eventuate in death, still run a not inconsiderable risk of having their life span shortened. It is further suggested that infected persons will experience more manifestations of general ill health than will those who have never had syphilis.

Immunity and Allergy in Syphilis.—Taking the point of view that penicillin may afford a new avenue to the understanding of the nature of immunity in syphilis, Urbach and Beerman¹⁰⁵ have reviewed the present status of immunity and allergy in syphilis. Their review does not readily lend itself to condensation. Exception might readily be taken to its primary premise. In summary it is concluded that:

1. Since penicillin has an apparent capacity to cure experimental and human syphilis quickly and completely, new fields for the experimental study of immunity in this disease are opened. This fact warrants critical reevaluation of the present status of immunity and allergy in syphilis.

2. According to the viewpoint adopted in this review, allergy is a comprehensive term which may be expressed as hyper- or hyposensitiveness, while immunity is a special form of allergic hypersensitiveness.

103. Bruusgaard, E.: Ueber das Schicksal der nicht spezifisch behandelten Luetiker, Arch. f. Dermat. u. Syph. **157**:309, 1929.

104. Deibert, A. V., and Bruyere, M. C.: Untreated Syphilis in the Male Negro: III. Evidence of Cardiovascular Abnormalities and Other Forms of Morbidity, J. Ven. Dis. Inform. **27**:301 (Dec.) 1946.

105. Urbach, E., and Beerman, H.: The Present Status of Immunity and Allergy in Syphilis, Am. J. Syph., Gonor. & Ven. Dis. **31**:192 (March) 1947.

some unexplained reason, the left side tends to be slightly more sensitive than the right side of the body. 4. Edema of the soft tissues interferes with the perception of vibration. 5. Paresthesias may confuse the results of the examination. In *tabes dorsalis*, the vibratory sensation was found to be strikingly lower than normal and to vary with the degree of damage at the time of examination. The level of the vibratory sensation was observed to rise as the patient's condition improved after successful treatment.

Charcot's Joints.—Historically, the etiology of that form of arthropathy known as Charcot's joint was the subject of a lively international controversy between the Frenchman, Charcot, and the German group of Volkmann and Virchow. Charcot believed that the changes in the joints were of a "trophic" nature whereas Volkmann took the position that they resulted from a multiplicity of subclinical traumatic insults to the joint which went unperceived because of the insensitivity of the affected joints. Delano,⁹³ who recently reviewed the subject of the pathogenesis of Charcot's joint, found no definitive evidence for the existence of trophic nerves and concurs in the Volkmann-Virchow concept. Commonly associated with late neurosyphilis of tabetic type, Charcot's arthropathy may occur also in syringomyelia and, more rarely, in trauma of the spinal cord, trauma of the posterior roots or peripheral nerves, tumors of the cord, congenital malformations (such as spina bifida), tuberculosis or malignant spondylitis, acute myelitis, poliomyelitis and diabetic pseudotabes. Both atrophic and hypertrophic forms of neuropathic arthropathy occur. Delano states the belief that the most characteristic feature of neuropathic arthropathies is endochondral ossification. Concomitantly there is resorption and endochondral proliferation of the bone, with resultant incongruity of the surface of the joint brought about by repeated subclinical traumas occurring in an insensitive joint.

In severe, poorly regulated diabetes mellitus of long duration there may be neurologic changes that closely mimic those of *tabes dorsalis* (diabetic pseudotabes). Sensory disturbances, evidences of damage to the posterior column, areflexia and a predilection for the lower extremities are common to both conditions. In further illustration of how closely similar syphilitic and diabetic neuropathy may be, Foster and Bassett⁹⁴ report 2 cases of severe diabetes of long standing in which there developed cord bladders and neurogenic arthropathy of the Charcot type. These authors suggest that dysfunction of the

93. Delano, P. J.: The Pathogenesis of Charcot's Joint, *Am. J. Roentgenol.* **56**:189 (Aug.) 1946.

94. Foster, D. B., and Bassett, R. C.: Neurogenic Arthropathy (Charcot Joint) Associated with Diabetic Neuropathy, *Arch. Neurol. & Psychiat.* **57**:173 (Feb.) 1947.

Book Reviews

A Textbook of Clinical Neurology. By J. M. Nielsen, M.D. Second edition. Price, \$7.50. Pp. 699. New York: Paul B. Hoeber, Inc., 1946.

Dr. Nielsen's "Textbook of Clinical Neurology" was published first in 1941; the revised second edition appeared in 1946. The author aimed to present the subject of clinical neurology in a volume sufficiently small that it could be used as a text of the subject during the time allotted to neurology in a general medical course. His goal has been accomplished and surpassed.

The routine material to be found in any good textbook of neurology is presented in most instances with acceptable detail. Comprehension of each subject is enhanced by discussions of the pertinent basic material in anatomy, physiology, pathology and pharmacology. Clinical appreciation of the subjects is increased by the author's creditable selection of brief case reports interspersed throughout the book. The book is well illustrated, well indexed and pleasingly made up. Furthermore, it is remarkably up-to-date. There is full discussion of the use of penicillin and sulfonamide compounds in the treatment of neurologic disorders.

The book is of particular importance because of the excellence of the material regarding cerebral localization and syndromes of the brain stem. Dr. Nielsen is an outstanding authority on aphasia, agnosia and apraxia. Only a thorough scholar could present these difficult subjects with the clarity and conciseness with which they are discussed in this book. Because of this fact, the textbook has surpassed the author's aim and will find its place in the reference library of actively practicing neurologists.

This book can be recommended without hesitation for medical students and for practitioners of medicine and surgery. Because it contains an excellent digest of the total information available on the subjects of agnosia, apraxia and aphasia, the specialists in neurology, neurosurgery and psychiatry will find it invaluable as a reference work.

Medicine in the Changing Order. Report of the New York Academy of Medicine, Committee on Medicine and the Changing Order. Price, \$2. Pp. 258. New York: Commonwealth Fund, 1947.

The committee of thirty-three physicians and seventeen representatives of allied professions and lay persons first convened on Feb. 25, 1943, and in a period of a little over three years has held one hundred and twenty-three meetings and has obtained information and opinion from a wide variety of authorities who "represented every shade of economic, social and political conviction that might have a bearing on medical care."

At the outset, the objectives were defined: "To be informed of the nature, quality and direction of the economic and social changes that are taking place now and that are clearly forecast for the immediate future; to define in particular how these changes are likely to affect medicine in its various aspects; to determine how the best elements in the science of medicine and in the services to the public may be preserved and embodied in whatever new social order may ultimately develop."

area, at least, it is considered that protection against neurosyphilis is afforded by coinfection with yaws, which is widely prevalent.

The relative significance of purely physiologic and emotional factors in the pathogenesis of the syndrome occurring after lumbar puncture has been studied by Redlich, Moore and Kimbell.¹⁰¹ One hundred hospitalized psychotic patients were subjected to routine lumbar punctures. Alternate patients were punctured with number 16 and number 22 gage needles. These two groups were comparable with respect to diagnosis, age, sex and ratings as to intelligence, mood, emotional stability, chronic anxiety and hypochondriacal trends. Reactions in patients punctured by the larger needle were definitely more frequent, more severe and longer lasting than those among patients punctured with the 22 gage needle. This is interpreted as an indication that leakage of cerebrospinal fluid plays the major role in the production of headache after puncture.

The occurrence of symptoms had no significant relationship to the intelligence or emotional stability of the patients. Those with normal moods seemed to suffer severer headaches than those who were depressed or elated. The presence of chronic anxiety or hypochondriasis predisposed to a slight increase in incidence of complications, but there was no increase in the number of severe reactions. Unlike the intrinsic personality traits of the patients, which did not significantly affect reactions, a knowledge of ill effects in others and anxiety with regard to the procedure did increase postpuncture sequelae to a significant degree.

The authors conclude that drainage is the most significant factor in the production of symptoms after lumbar puncture, outweighing by far the small contribution of anxiety, hypochondriasis and other emotional elements.

The Outcome of Untreated Syphilis.—The end results of untreated syphilis are discussed by Rosahn¹⁰² in the latest of his significant retrospective studies made at the Yale University School of Medicine. Among 380 syphilitic patients who were examined at autopsy at the New Haven Hospital in the period of 1917 to 1941 there were 198 (52.1 per cent) who had received no antisiphilitic therapy. Anatomic lesions of syphilis were found in 77 (38.9 per cent) of the untreated patients, but only 23.2 per cent of the entire group died primarily as a result of syphilis. Histopathologic evidences of syphilis were absent in 121 patients (61.1 per cent). Of these, 80 had serologic evidence

101. Redlich, F. C.; Moore, B. E., and Kimbell, I., Jr.: Lumbar Puncture Reactions: Relative Importance of Physiological and Psychological Factors, *Psychosom. Med.* 8:386 (Nov.-Dec.) 1946.

102. Rosahn, P. D.: Studies in Syphilis: VII. The End Results of Untreated Syphilis, *J. Ven. Dis. Inform.* 27:293 (Dec.) 1946.

The inclusion of two new chapters in the second edition of this volume, one dealing with the thyroid by Alexander Winkler and the other with the diseases of the kidneys by Max Miller and Joseph Hayman, may be of doubtful wisdom. The chapters are well written, but to the extent that the material involves metabolic abnormality it represents some repetition of what appears in other chapters and to the extent that it involves morphology it may be out of place in such a book as this. At least as good a case might be made for adding chapters on diseases of the liver, on pregnancy, on growth and development in childhood and on diseases of the nervous system with components which are metabolic.

The first edition of this book was well received. The second edition brings the subjects up to date and can be highly recommended. Charles Best has stated in its foreword that "we are at the threshold of what may prove to be a great new era in metabolic and other aspects of medical research. It is essential, therefore, for us to make critical appraisal of our present knowledge of metabolic processes. There is no doubt that we have a firm foundation on which to build, and many lofty structures have already been erected. A few, however, may be picturesque but unsound, and a review of the situation such as that provided in this new edition of 'Diseases of Metabolism' comes at an opportune time."

Medical Aspects of Growing Old. By A. T. Todd, M.B. Price, 15s. Pp. 172. Baltimore and Bristol, England: John Wright & Sons, 1946.

It seems recently to have become the fashion for medical men of a certain age to emulate Cicero and write about old age. Considerable geriatric literature has accumulated on this side of the Atlantic; here is a British sample.

The author writes pleasantly on the medical aspects of growing old and, on the whole, tends to show that the experience of adding years to one's life may be made into an amiable adventure if it is handled properly. He gives sensible advice in regard to the care of ancient hearts, blood vessels and digestive tracts and even of well worn hands, feet and skin. He has a nice philosophy, well expressed. He has prepared an attractive monograph which both patients and their physicians can study with profit.

Précis de virologie médicale: Vaccine-variole, herpès, encéphalites, rage, poliomyélite, chorio-méningite, fièvre jaune, psittacose, influenza, maladie de Nicolas et Favre, nature et genèse des ultravirus, techniques. By C. Levaditi. Paper. Price, 235 francs. Pp. 250, with 142 illustrations. Paris: Masson & Cie, 1945.

This book has as its main purpose the condensed presentation of the knowledge on the most important virus infections of man, followed by a discussion of the nature of viruses. A chapter of thirty-six pages on the technics employed in the study of virus infection is too concise and incomplete to be useful. Although it goes into detail about stains and staining solutions, the use of filters and method of infection, it completely ignores the serologic diagnostic procedures. There is no bibliography except an occasional footnote referring the reader to the handbook "Les ultravirus des maladies humaines," published in 1938 by the same author in collaboration with P. Lépine.

In accordance with the well known views of the author, the infections are grouped under the following headings; pure ectodermoses (vaccinia), neurotropic ectodermoses (herpes, encephalitis), neuroses (rabies, poliomyelitis), neuro-organotropic virus diseases (yellow fever), viscerotropic virus diseases (psittacosis, influenza) and mesodermotropic virus diseases (lymphogranuloma).

3. In syphilis there are two types of immunity; (a) natural resistance and (b) acquired immunity. Human beings are naturally susceptible to syphilis, while many species of animals previously thought to enjoy natural resistance are really susceptible but acquire only an asymptomatic infection.

4. All authorities agree that variable grades of immunity develop in syphilitic animals and man; but opinion is divided as to whether this immune state depends on persistence of infection (Neisser, Kolle) or whether it is independent of it (Chesney).

5. Under certain experimental conditions and taking account of the various modifying factors, the untreated animal, as determined by the results of reinoculation, acquires resistance to a second infection slowly. During the early phases of the disease untreated animals are wholly receptive to a new infection, later they are not. In animals treated early, prior to the development of immunity, second infection is manifested by chancre formation. Energetic treatment in late syphilis will protect the animals against reinfection. It is suggested that a controlled repetition of these experiments, using penicillin as the means of cure of syphilis because of its rapid excretion, would throw light on the nature of syphilis immunity.

6. Attempts to superinfect untreated syphilitic individuals with massive inoculums are often successful. This indicates that their immunity is at best only relative in all phases of the disease. This fact brands efforts to immunize syphilitics with virulent treponemes as potentially dangerous.

7. Intensive treatment of early syphilis will probably cure the disease. Though such treatment abolishes developing immunity, it does not subject the patient to danger if the treatment completely eradicates the disease. If therapy is inadequate, it leaves the patient in a vulnerable position since the developing defenses are disturbed and the patient is not cured. This state often results in various forms of therapy-resistance or seroresistance.

8. The mere fact that a patient may be reinoculated successfully with syphilis does not indicate that he has been cured. On the other hand, completely cured individuals may remain refractory to reinfection.

9. In patients treated early in the course of syphilis, reinfection does not indicate cure since it may be possible that the new infection could be superinfection. We have no adequate means of differentiation between reinfection and superinfection.

10. Allergy and immunity are not mutually exclusive, but immunity is a special aspect of allergy. This viewpoint is upheld by various experimental studies. The entire course of syphilis may be explained on the basis of allergy. The reaction of the organism to reinfection also suggests an allergic mechanism. Attempts to develop a method to determine the allergic state of a syphilitic individual have led to little of a definite nature. While culture luetin is diagnostically worthless, reevaluation of organic luetin is suggested.

11. The question of the existence of antibodies against syphilis is still unanswered, but recent work suggests a cellular defense. The relationship of the positive serologic reaction to the organism's capacity to produce antibodies against spirochetes is not clear.

12. Numerous attempts to induce active or passive immunization against syphilis in man and animals have to date failed to produce any significant results. This applies both to prevention of the infection as well as to the treatment of an established syphilitic infection."

(To Be Continued)

period, indefinite in time, only the fibroblastic elements survive and start a copious proliferation, as they are by then completely adjusted to the new medium. The proliferative and maturative changes of the specific elements are particularly evident in the surviving cells of the erythroblastic and granuloblastic series. Parent cells of the monocytic and lymphocytic series and megakaryocytes, however, do not show any tendency to proliferation.

The main feature of this work is represented by the developed technic, which is particularly promising of results in the study of several known and unknown factors in the evolution and proliferation of living marrow elements.

Le malattie del sangue (Pathology of the Blood). By A. Ferratta, M.D., and E. Storti, M.D. Price not stated. Pp. 751, with 295 illustrations. Milan, Italy: Societa Editrice Libreria, 1947.

This manual, while written by two Italian physicians, might well have been prepared for American readers. Perhaps it merely reveals the international uniformity of medical opinion now existing in regard to the diagnosis and treatment of the various disorders of the blood. In either event, the result is satisfactory.

The book begins with an account of how blood is formed and how it functions. It next discusses finer points regarding blood counting. This is followed by excellent descriptions of bone marrow histology, blood transfusion, blood typing and methods of estimating the sedimentation rate. Most of the volume, however, deals with matters that are more strictly clinical in nature. The anemias, the leukemias and the reaction of the blood-forming organs to onsets of varying kinds are discussed in detail, both diagnosis and treatment receiving ample consideration. Many exceptionally good illustrations and colored plates embellish the text and make it all the easier to understand.

The end result is an attractive textbook. It is certain to be appreciated by the physicians and medical students for whose benefit it was composed.

A Color Atlas of Hematology. By Roy R. Kracke, M.D. Price, \$5. Philadelphia: J. B. Lippincott Company, 1947.

As stated in the preface, this book was prepared especially for the use of medical students, laboratory technicians and general practitioners. The author has achieved his purpose in an eminently satisfactory manner. Although the volume has been kept to a small, convenient size, all the important variations in both normal and abnormal blood pictures are shown in the 32 color plates. Adding greatly to the usefulness of this type of atlas is a concise, systematic clinical discussion of the various blood diseases. Valuable chapters have been included on hematologic technics, the bone marrow, blood parasites, splenomegaly and splenectomy, the blood picture in various laboratory animals, hematologic definitions and, finally, a "summary of hematologic findings in various diseases and conditions."

This is an excellent practical atlas and concise summary of present day hematology by a recognized authority. It should prove of value to all those concerned with this subject.

Biological Symposia: A Series of Volumes Devoted to Current Symposia in the Field of Biology. Volume 12: Estimation of the Vitamins, edited by J. D. Dann and G. Howard Satterfield. Price, \$6.50. New York: The Ronald Press Co., 1947.

This is an advanced book for the specialist. It consists of a series of articles by experts describing in technical terms the various methods of vitamin assay—

The report is condensed into twelve chapters, which begin with a historical discussion of the origins of the present problems in American medicine, particularly in recent decades, and go on to a discussion of the health of the nation, medical care in urban and in rural areas, extension in public health services, quality of medical care, preventive medicine, the hospital, nursing, medical insurance—voluntary and compulsory—and a final statement of the methods and the goal.

The committee is to be commended for its broad-gaged study of this most complex and vital problem and also for its soundness in the formulation of recommendations which deserve the full support and careful consideration of all the members of the medical profession.

Diseases of Metabolism: Detailed Methods of Diagnosis and Treatment.

Edited by Garfield G. Duncan, M.D. Second edition. Price, \$12. Pp. 1045, with 167 illustrations. Philadelphia and London: W. B. Saunders Company, 1947.

It is difficult to circumscribe that part of medicine which deals with metabolism. Metabolism includes all those processes by which matter, be it organic or inorganic, is utilized for the growth, repair and maintenance of the organism. The processes comprehend intake of food, including minerals, water and other factors, such as vitamins; transportation of oxygen, and the manifold chemical transformations of organic materials whereby energy is released as heat and the activities of muscles, nerves and glandular organs are maintained and waste products are disposed of by excretion through lungs, kidneys, skin and bowel. Therefore every field of medicine is invaded, and, in truth, as the search for understanding of the metabolic abnormalities in disease and injury has extended, light has been brought to bear on obscure problems of each of the several specialties of medicine and surgery.

Duncan and the outstanding collaborating authors have provided in this volume a satisfactory appraisal of the present state of knowledge of the metabolic aspects of disease. The scientific background is adequately reviewed, but such material as has little practical application at the present was omitted in this second edition. Emphasis is placed on the significance of metabolism in diagnosis and treatment, and yet the bridging of the gap between the scientist and the physician is adequately effected.

Duncan is himself responsible for the chapters on exchange of energy (general and basal metabolism), diabetes mellitus, hyperinsulinism and diabetes insipidus. The metabolism of sugar and other carbohydrates is reviewed by C. N. H. Long and that of protein and the lipids by Abraham White. Mineral metabolism is discussed by Abraham Cantarow. His chapter also covers hyperparathyroidism and hypoparathyroidism, adrenocortical insufficiency (Addison's disease) and adrenocortical hyperfunction. Water and acid-base equilibrium are reviewed by John P. Peters, with special attention given to edema, the salt depletion of pneumonia, the nature of "shock" and the effects on salt and water metabolism of heart failure, disease of the kidneys and disease and disorder of the gastrointestinal tract.

The diagnostic problems presented by diseases of the blood are largely morphologic, but the etiology and treatment of many of these diseases present problems of nutrition and metabolism. The diseases of the blood receive consideration from this aspect by L. M. Tocantins. Vitamins and vitamin deficiencies are reviewed by T. D. Spies and H. R. Butt; undernutrition is discussed by L. H. Newburgh, and obesity, by Frank Evans. The chapter on gout is by Walter Bauer and Frederick Klemperer, and the one on xanthomatosis, glycogen disease and other disturbances of intermediary metabolism, alkaptonuria, porphyria and the like is by E. U. Mason.

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FIFTEEN YEARS' EXPERIENCE WITH FREE FEEDING OF PATIENTS WITH BLEEDING PEPTIC ULCER

Fatal Cases

E. MEULENGRACHT, M.D.

COPENHAGEN, DENMARK

FIFTEEN years ago I introduced the "free feeding program" in the treatment of bleeding peptic ulcer, or gross hemorrhage with hematemesis and melena.¹ Since then I have consistently followed the recommendations laid down at that time for the treatment and have repeatedly summarized my material and reported on the results obtained.²

The method has been adopted in most countries, and numerous publications dealing with their authors' experiences have appeared. I am unable to give an exhaustive review of the literature on the subject at the present time, particularly with regard to the English and American articles, because, as a result of Denmark's isolation during the war, gaps in the series of periodicals occurred and they have not yet been brought up to date. But as far as I can make out, general agreement on the advantages of the treatment prevails among all those who have had experience with it. There is a consensus that this treatment means an enormous simplification in the care of the patients. Further, they are spared tantalizing discomforts in the form of immobilization, hunger and thirst, and it is therefore much more acceptable to them. It is also agreed that the patients recover more rapidly from hemorrhagic shock, that the general condition quickly improves or at any rate in no way deteriorates and that blood regeneration proceeds at a greater speed. It is also allowed that the tendency to hemorrhage is not increased by food entering the stomach. Some assume that the reason for this is the diminution in the hunger contractions of the stomach. Others connect it with the neutralization of the gastric juice. Whatever the explanation given, that the bleeding is not intensified is accepted as a fact. Some even assert that it is lessened.

From the Medical Clinic B at Bispebjerg Hospital.

1. Meulengracht, E.: *Ugesk. f. læger* **95**:1257, 1933; *Acta med. Scandinav.* (supp.) **59**:375, 1934; *Klin. Wchnschr.* **13**:49, 1934.

2. Meulengracht, E.: *Lancet* **2**:1220, 1935; *Wien. klin. Wchnschr.* **49**:1481, 1936; *München. med. Wchnschr.* **84**:1565, 1937; *Brit. M. J.* **2**:321, 1939.

The author's theories are given prominence. For example, he concludes that postvaccinal encephalitis is a complication brought about in predisposed persons by the localization of an unknown virus in the central nervous system. The allergic phase present in vaccination is considered to be particularly favorable to the encephalic genesis of the process. The discussion of herpes simplex overlooks the present day knowledge of the ecology of this virus. On page 136 Levaditi dogmatically says: "It is certain that the virus of poliomyelitis invades the body through the upper respiratory tract and, in particular, the nasopharyngeal mucosa, and it is likewise eliminated through this mucosa."

More than twenty-one pages are devoted to a presentation of the subject of *ultravirus lymphogranulomateux (maladie de Nicolas et Favre)*, while the discussion on influenza covers but eight pages. Equally brief is the chapter on yellow fever, which incompletely reports the fascinating epidemiologic studies on jungle yellow fever. In fact, the whole treatise is singularly deficient in epidemiologic thinking. But such criticism is really immaterial, because the merit of the compendium lies in the summary presentation which acquaints the reader with the rapidly growing field of virus agents that are believed to cause infections or infectious diseases.

Until a similar up-to-date book in the English language is available, students and physicians may enjoy this presentation of the subject.

On the Morphology of Blood and Bone-Marrow in Thyrotoxicosis. Inaugural Dissertation. By O. Biström. Pp. 188. Acta chirurgica Scandinavica, volume LXCIV, supplementum 114. Stockholm: Norstedt & Söner, 1946.

This monograph is a report of the condition of the blood and of the bone marrow obtained by aspiration in 24 control subjects, 26 patients with nontoxic goiter and 33 patients with thyrotoxicosis. The older literature is completely reviewed; practically no investigations have been reported on the bone marrow in thyrotoxicosis.

The patients with nontoxic goiter showed no important abnormalities. The more important deviations in the patients with thyrotoxicosis consisted of a lymphocytosis of the peripheral blood and a shift toward immaturity of the neutrophilic granulocytes and, to a lesser extent, of the normoblasts in the bone marrow. This shift was more distinct in the severely toxic forms of the disease. The described changes reverted toward normal after therapy with iodine or methylthiouracil and after thyroidectomy. The author does not feel that the inconstant and slight changes in the blood and bone marrow are of great importance in the prognosis and diagnosis of thyrotoxicosis. The monograph should be a useful reference for workers in this field.

La cultura in vitro del midollo osseo. By Aminta Fieschi and Giovanni Astaldi. Pp. 309, with 122 illustrations, 10 in color. Pavia, Italy; Tipografia del Libro di S. Bianchi, 1946.

A new technic of culture suspension of heparinized bone marrow is suggested. It consists in the use of a simple apparatus that permits a regular supply of oxygen and nutritive material to the cultured marrow. Tyrode's solution is homologous fresh plasma and extraction of chicken embryo circulated through a system in which waste products are removed. Cultures of normal and abnormal human bone marrow have been carried out with this technic.

When normal bone marrow is so cultured, it may be observed that in the first eight to fifteen days both specific marrow cells and fibroblasts are present in the tissue and will survive and show signs of moderate proliferation. In the second

TREATMENT BY PROMPT AND FREQUENT FEEDING

From the first day after their admission to the hospital the patients are given a full "purée diet." The diet includes the following meals: at 6 a. m. tea, white bread and butter, at 9 a. m. oatmeal porridge with milk, white bread and butter, at 1 p. m. dinner, at 3 p. m. milk or cocoa and at 6 p. m. egg, sandwiches, sliced meat, cheese and tea.

The dinner includes a variety of dishes, e.g., different kinds of gruel, porridge, vegetable soups, meat balls, timbale, stewed chops, omelette, fish balls, vegetables au gratin, meat au gratin, fish au gratin, mashed potatoes, vegetable purées, creamed vegetables, stewed apricots, apple sauce and rice and tapioca puddings. The patients are allowed to have as much as they want.

Water and milk are put on the table for free use, and the patients are urged to drink as much as they feel inclined to.

Ferrous tartrate is given in a dose of 0.5 Gm. three times daily. At first alkali and belladonna were also administered, but the use of these is now restricted to patients with cardialgia, which is only rarely present. In severe cases a blood transfusion is given.

It is rather at random that I have chosen the purée diet. One can just as well adopt any other form of bland and nonirritating diet based on the culinary customs of the particular locality. It is more a question of adhering to the principle of something to eat and drink from the first day and a varied and liberal diet given in frequent meals.

MATERIAL UP TO THE PRESENT TIME

In the intervening years since June 1, 1931, when I changed over to the free feeding program as a routine measure, up to June 1, 1946, I have treated a total of 1,031 patients with bleeding gastric ulcer according to these principles. The material comprises 1,005 patients discharged from hospital after completion of the treatment and 26 who died as a near or remote result of the hemorrhage, that is to say, while in hospital.

The 1,031 patients include all those with bleeding gastric ulcer who were admitted to Medical Clinic B at Bispebjerg Hospital in Copenhagen during the period mentioned. This is a municipal hospital, and in Copenhagen hospital conditions are such that practically all patients in whom hematemesis or obvious melena develops are regarded as "nonrejectable" and are admitted immediately.

The material comprises only patients with gross hemorrhage, i.e., distinct hematemesis or directly visible melena. Patients with small quantities of blood in the vomitus ("hematemesis spuria") or with only chemically detectable melena are excluded. Also excluded are patients

chemical, biologic and microbiologic. There are comprehensive bibliographies. This treatise should be invaluable to those working in the special field of vitamin measurements, since not only is theory discussed but minute directions for the practical procedures are given.

Urology in General Practice. By N. F. Ockerblad, M.D. Second edition. Price, \$5.75. Pp. 392, with illustrations. Chicago: Year Book Publishers, Inc., 1947.

This little treatise attempts to present in simple terms the problems of urology which confront the general physician. Special problems of surgical technic and the like are not gone into. The discussions are brief and simple and to the reviewer seem useful. For example, a chapter on "catheters and sounds—their uses and dangers" can surely be read with profit. Some of the material on medical problems, such as nephritis, is sketchy and perhaps less useful. The book is well illustrated and has an index.

Diseases of the Chest with Emphasis on X-Ray Diagnosis. By Eli H. Rubin, M.D. Price, \$12. Pp. 685, with 355 illustrations. Philadelphia: W. B. Saunders Company, 1947.

This treatise discusses comprehensively the various diseases which affect the structures within the chest. Thus there are included not only such processes as tumors, abscess and bronchiectasis but also conditions like acute pneumonia and bronchial asthma. Pulmonary tuberculosis is thoroughly gone into, although only a small paragraph is devoted to streptomycin, which is so much to the fore today. The anatomy and physiology of the lungs are adequately discussed, and the sections on surgical procedures are useful. As Dr. Rubin points out, roentgen diagnosis is emphasized, and there are over three hundred admirable reproductions of roentgenograms dealing with every sort of pulmonary disease. This is an unusual and certainly invaluable feature of the book.

Asma alergia. By Guido Ruiz Moreno, M.D. Pp. 186. Buenos Aires, Argentina: Lopez & Etchegoyen, S. R. L., 1947.

This book has been written for students as an introduction to the more extensive textbooks on the subject and for general practitioners as a contemporaneous orientation.

The work is divided into two parts. The first section is devoted to a discussion of asthma. The definition, classification, physiopathology, symptomatology and etiology of the asthmatic states are discussed. There are also in this section discussions on the diagnosis, prognosis, treatment, complications and sequelae of asthma. The author included in this section a discussion of asthma as a problem in social medicine. In the second part the definition, concept and classification of allergies are discussed. There are brief general discussions on the clinical aspects of allergic diseases.

Each chapter is followed by a brief outline in which the essentials of the particular subjects are summarized. Dr. Moreno's observations on asthma and the clinical allergies have been made in Argentina and should prove of definite value to the physicians of that country.

The result is roughly the same when the duration of the time in hospital until the occurrence of death is considered (table 4).

Pathologic Condition.—On clinical examination a series of complicating diseases was detected. In most cases, however, the investigation was conducted in unfavorable circumstances, and the postmortem examination therefore affords a better basis for determining the condition.

At autopsy as many ulcers were found to be located in the stomach as in the duodenum.

From the pathologic-anatomic standpoint all the ulcers gave the impression of being chronic. Ten were extremely large, reaching the size of up to half the palm of the hand. In 4 patients two or three ulcers were present at the same time. Most of the ulcers in the stomach were penetrating. Three penetrated to the pancreas, one to the pancreas and liver and one to the omentum. In 1 case there was threatened perforation. Of the duodenal ulcers, one had penetrated to the pancreas—resulting in an abscessed cavity in the pancreas and localized fibrino-purulent peritonitis around the stomach—and to the liver and spleen, one had penetrated to the liver and in one the perforation had caused an abscess cavity behind the stomach, which reached downward around the left kidney and upward under the diaphragm and had passed through to the left pleura. Of the jejunal ulcers, one had penetrated to the thoracic wall, while in one there was an open perforation with diffuse purulent peritonitis.

In 17 cases eroded vessels of various sizes were found, most of which appeared to be arteries.

At the autopsies a number of serious complicating diseases were also discovered i.e., arteriosclerosis, fibrosis of the myocardium, cardiac hypertrophy, syphilitic aortitis, aortic aneurysm, pleuropneumonia, embolus of the pulmonary artery, sclerotic kidney and hypertrophy of the prostate.

The Immediate Cause of Death.—The immediate cause of death in the 26 fatal cases is given in table 6.

Two patients died from a large embolus in the pulmonary artery on the sixth and twenty-seventh days respectively after the onset of the hemorrhage and at a time, moreover, when they were improving. The first patient had previously been bedridden on account of prostatic disease. One patient died from diffuse peritonitis following an undiagnosed perforation and 1 from a perforation associated with a large subdiaphragmatic abscess which had infiltrated the tissues and reached the pleura. In 1 hemorrhage and perforation were considered to have had an equal share in causing death, and in another there was extensive lobar pneumonia with a large pleural exudate as well as the hemorrhage.

It is further agreed that the mortality rate is decreased, which, of course, is the crucial point. However, there is a difference of opinion as to the extent to which it can be lowered. In the United States fairly extensive reports have been published by Nicholson and Miller³ as well as by Rasberry and Miller.⁴ In their collected material, comprising 2,111 cases, they obtained a gross mortality of 4 per cent and a net mortality of 1.9 per cent, the latter figure implying that patients with cancer and perforations and moribund patients who never received the treatment were excluded. Subsequently, Miller's⁵ own net mortality figure was only 1 per cent.⁵ They set this figure against the mortality rate of 8.7 per cent found by Miller and Elsom⁶ among 5,843 patients treated on the old principles of immobilization administration of morphine and starvation (according to Schiff⁷ it ought to be 9.1 per cent). The figures, however, vary a good deal from one locality to another, perhaps partly because the number who undergo treatment in a hospital varies extraordinarily in different places.

These records agree fairly well with the Scandinavian figures. Thus when I introduced the treatment in 1931, I found that the mortality rate fell to within 1 to 2 per cent from the 8 to 10 per cent which had previously been the general figure for mortality in Scandinavia for corresponding material treated by the older method (immobilization, administration of morphine and starvation).

It must be pointed out that such a difference would hardly be obtained today. In the course of the later decades, at all events in Denmark, a change in the character of the peptic ulcer has taken place, with the result that the mortality of bleeding peptic ulcer has decreased intrinsically. This question is fully discussed by Alsted⁸ in his book, "Changing Incidence of Peptic Ulcer." From this it appears that peptic ulcer has gradually become rarer in women and commoner in men and that the occurrence of gastric ulcer has become less frequent and that of duodenal ulcer more so ("the ulcers have moved down towards the duodenum"). Simultaneously, hemorrhage has become more frequent but possibly less severe. These facts naturally cannot be ignored in a comparison of older material with that of the present day.

3. Nicholson, I. T. L., and Miller, T. G.: *Am. J. Digest. Dis.* **8**:446, 1941.

4. Rasberry, E. A., and Miller, T. G.: *Gastroenterology* **1**:911, 1943.

5. Miller, T. G.: *South. Med. & Surg.* **107**:54, 1945.

6. Miller, T. G., and Elsom, K. A.: *M. Clin. North America* **22**:1711, 1938.

7. Schiff, L.: *South. M. J.* **37**:335, 1944.

8. Alsted, G.: *Changing Incidence of Peptic Ulcer*, London, Oxford University Press, 1939.

1939	M	53	10 yr.	Hematemesis and melena	Within 1 day	9 days	Two small chronic duodenal ulcers; large eroded blood vessel; coronary arteriosclerosis; cardiac hypertrophy	Repeated bleeding
1940	F	82	?	Hematemesis and melena	Within 1 day	2 days	Two small chronic duodenal ulcers; arteriosclerosis; fibrosis of the myocardium	Persistent bleeding
1940	M	73	6 yr.	Hematemesis and melena	8 days	27 days	Chronic ulcer of the pylorus, 2 by 2 cm.; thrombophlebitis of the lower extremities; thrombophlebitis of the inferior vena cava; embolus of the pulmonary artery; fibrosis of the myocardium; renal sclerosis; hypertrophy of the prostate	Embolus of the pulmonary artery
1941	F	68	6 mo.	Hematemesis and melena	2 days	3 days	Chronic ulcer, 5 by 7 cm., on the lesser curvature penetrating to the liver and the pancreas; large eroded blood vessel; large left-sided pleuropneumonia; thrombosis of the pulmonary artery; arteriosclerosis; fibrosis of the myocardium	Pleuropneumonia; repeated bleeding (?)
1942	F	75	2 yr.	Hematemesis and melena	5 days	3 days	Chronic duodenal ulcer, 1 by 1 cm.; eroded blood vessel; arteriosclerosis; fibrosis of the myocardium	Persistent or repeated bleeding
1943	M	57	6 yr.	Hematemesis and melena	Within 1 day	2 days	Chronic ulcer, 1 by 1 cm.; eroded blood vessel	Persistent bleeding
1943	M	47	Many years	Hematemesis	2 days	2 days	Gastroenterostomy; gastrojejunal ulcer penetrating to the abdominal wall; fibrosis of the myocardium; cardiac hypertrophy; renal sclerosis	Repeated bleeding
1943	M	67	25 yr.	Hematemesis and melena	Within 1 day	5 days	Gastroenterostomy; three small chronic duodenal ulcers; large embolus of the pulmonary artery; arteriosclerosis; fibrosis of the myocardium; hypertrophy of the prostate	Embolus of the pulmonary artery
1944	M	26	0	Hematemesis and melena	Within 1 day	10 days	Chronic duodenal ulcer, 2 by 3 cm., eroded blood vessel; syringomyelia	Repeated bleeding
1944	M	70	12 yr.	Hematemesis and melena	Within 1 day	2 days	Chronic duodenal ulcer, 2 by 2 cm.; eroded blood vessel; arteriosclerosis	Persistent bleeding
1944	M	58	2 yr. (?)	Hematemesis and melena	10 days	12 days	Chronic duodenal ulcer, 4 by 5 cm., penetrating to the liver; large eroded blood vessel; syphilitic aortitis; aortic aneurysm	Repeated bleeding
1944	F	71	Several years	Hematemesis and melena	Within 1 day	5 days	Ulcer, 1 by 1 cm., on the lesser curvature, with threatened perforation; eroded blood vessel; arteriosclerosis; cardiac hypertrophy; fibrosis of the myocardium	Repeated bleeding and cerebral thrombosis
1945	F	78	30 to 40 yr.	Hematemesis and melena	Within 1 day	3 days	Gastroenterostomy; 5 by 5 cm. and 1 by 1 cm. chronic ulcers on the lesser curvature; 1 by 1 cm. chronic duodenal ulcer perforating to a large abscess cavity; the abscess lies behind the stomach and extends upward under the diaphragm and downward to the left kidney, and there is passage through to the left pleura; arteriosclerosis; fibrosis of the myocardium	Perforation and sub-diaphragmatic abscess

who had hemorrhage due to carcinoma of the gastrointestinal tract or to esophageal varicose veins in cirrhosis of the liver or to other diseases which have no connection with peptic ulcers or "ulcer disease." In the case of the discharged patients this was ensured, so far as was possible, with the help of the clinical picture and the course of the disease and in the fatal cases by the fact that a postmortem examination was made of all the patients who died during the period concerned from, or partly from, hematemesis or melena.

There remains then a total number of 1,031 patients, including 26 who died, in whom the hemorrhage was regarded as arising from peptic ulcer or "ulcer disease."

FATAL CASES

The 26 fatal cases were subjected to further investigation.

Sex and Age.—There were 17 men and 9 women, and the age varied from 26 to 86 years. It is worth noting that 25 of the 26 patients were over 40 years of age and half of these were over 60 (table 1).

The patients who died thus belong to the higher age groups.

TABLE 1.—*Distribution of the Patients Who Died According to Age*

Age.....	Under 40	40 to 50	50 to 60	60 to 70	70 to 80	Over 80
No.....	1	6	6	4	7	2

History of Ulcer.—In the investigation of the history it was striking, in view of the fact that at autopsy chronic and often large and deep ulcers were demonstrated, that some of the patients seemed to lack a genuine history of ulcer. Without doubt this was partly because the history was taken on admission of the patients to the hospital, when they had sustained mental or physical shock from hematemesis and loss of blood, with the result that the information was not always absolutely reliable.

Hematemesis or Melena.—In all 26 cases the hemorrhage made its presence known as hematemesis. Usually there was also melena, but some patients did not exhibit this symptom. The hematemesis was most often of a severe type.

The Time of Supervention of Death.—In all 26 cases there was accurate information as to when the bleeding began. In 17 it started immediately before admission to the hospital, that is, within twenty-four hours. In 1 it began eight days, in another ten days and in the remainder a few days before admission. One can thus determine the time which elapsed between the onset of the bleeding and the occurrence of death (table 3).

compensatory sclerosis of the kidneys and 1 noncompensatory sclerosis of the kidneys and uremia. Even if these conditions in themselves would not have caused death at the stage in question, it is clear that their presence rendered the patients less able to withstand the hemorrhage.

Mortality.—If the number of patients who died from, or partly from, the hemorrhage, i.e., while in hospital, is to be calculated, the figures 1,031 and 26 must be used, and a gross mortality of 2.5 per cent is obtained.

If patients are excluded whose deaths were entirely or in the main due to causes other than bleeding (embolus of the pulmonary artery, 2 patients; perforation and peritonitis, 2 patients; pleuropneumonia, 1 patient; thrombosis [hemorrhage?] of the brain, 1 patient) as well as those who died within twenty-four hours of admission (one, eight, fifteen, twenty-two and twenty-three hours respectively) and had therefore not received the treatment, a net mortality of 1.5 per cent is obtained.

COMMENT

An analysis of the fatal cases discloses that there was a definite preponderance of deaths in the older age groups. The average age of the 26 patients was 57 years; 96 per cent were over 40 and 50 per cent over 60. In contrast to this, the majority of the patients in my collected material belong to the lower age groups. In an earlier study (1935) Rischel found an average age of 48 years; 66 per cent were over 40 and 23 per cent over 60.

This therefore signifies that the risk of hemorrhage in the free feeding program is greatest in the higher age groups, which is presumably due to the poor condition of the vessels and the various complicating diseases in those age groups. In patients under 40 years of age the risk is clearly slight. The same risk in the higher age groups is present also with other forms of treatment. Hansen and Pedersen⁹ thus found that of 393 patients with fatal hematemesis and melena in Copenhagen hospitals during the period 1915 to 1937, 87 per cent were over 40 years of age, and the largest number of deaths involved patients 60 to 69 years of age.

In all the fatal cases the bleeding manifested itself as hematemesis. The frequency of hematemesis was far greater among the fatal cases than in my collected material. Rischel¹⁰ noted hematemesis one hundred and twelve times and melena ninety-four times. In extensive collected material from Copenhagen hospitals during the period 1925 to 1935 Alsted⁸ found that in 684 cases the bleeding had manifested itself as melena. Since then there has been a change in the direction of the still rarer occurrence of hematemesis.

9. Hansen, J. L., and Pedersen, J.: *Nord. med.* 7:1567, 1940.

10. Rischel, A.: *Klin. Wchnschr.* 15:335, 1936.

TABLE 2.—Data on the Twenty-Six Fatal Cases

Year	Sex	Age, Years	Duration of Ulcer Symptoms	Manifestation of Hemorrhage	Interval Between First Appearance of Hemorrhage and Admission to Hospital	Interval Between Admission to Hospital and Death	Postmortem Findings	Cause of Death
1931	M	45	6 yr.	Hematemesis and melena	1 day (6 days?)	6 days	Scar on the lesser curvature; gastroentero-anastomosis; perforated peptic ulcer of the jejunum; diffuse purulent peritonitis; stenosis and incompetence of the aortic valves; hypertrophy of the heart; renal sclerosis	Perforation and diffuse peritonitis
1933	M	50	? (moribund)	Hematemesis and melena	2 days	Immediately after admission	Chronic juxtapiyloric ulcer; 2 by 2 cm.; walnut-sized abscess in the right lung	Persistent bleeding
1933	M	50	1 yr. (?)	Hematemesis and melena	8 days	17 days	Chronic duodenal ulcer, 3 by 3 cm.; large eroded blood vessel; renal sclerosis; hypertrophy and fibrosis of the myocardium	Repeated bleeding, renal sclerosis and uremia
1934	F	76	1 yr. (?)	Hematemesis and melena	1 day	Within 1 day	Chronic ulcer, 6 by 6 cm.; penetrating to the pancreas; two eroded blood vessels; arteriosclerosis; fibrosis of the myocardium	Persistent bleeding
1936	M	40	2 wk.	Hematemesis and melena	5 days	7 days	Chronic ulcer, 5 by 4 cm., on the lesser curvature penetrating to the pancreas; two or three eroded blood vessels	Persistent or repeated bleeding
1936	F	74	2 yr. (?)	Hematemesis and melena	Within 1 day	6 days	Chronic ulcer, 2 by 2 cm., on the lesser curvature; large eroded blood vessel; arteriosclerosis	Repeated bleeding
1937	M	45	15 yr.	Hematemesis and melena	Within 1 day	1 day	Duodenal ulcer, 3 by 3 cm., penetrating to the pancreas; two or three eroded blood vessels; pyloric stenosis; abscess cavity in the pancreas and fibrinopurulent peritonitis around the stomach, liver and spleen	Persistent bleeding and localized fibrinopurulent peritonitis
1937	M	48	10 yr.	Hematemesis	1 day	7 days	Chronic duodenal ulcer, 1 by 2 cm.; pyloric stenosis	Repeated bleeding
1937	M	86	15 yr.	Hematemesis	Within 1 day	Within 1 day	Chronic ulcer, 5 by 5 cm., just before the pylorus penetrating to the pancreas; large eroded blood vessel; arteriosclerosis	Persistent bleeding
1938	F	59	0	Hematemesis and melena	1 day	1 day	Ulcer of the pylorus, 4 by 6 cm.; eroded blood vessel; mammary carcinoma	Persistent bleeding
1938	M	46	2 mo.	Hematemesis	Within 1 day	2 days	Chronic ulcer, 4 by 4 cm., in the stomach on the posterior wall near the pylorus penetrating to the omentum; large eroded blood vessel; 1 by 1 cm. ulcer in the stomach on the posterior wall	Persistent or repeated bleeding
1938	M	66	10 yr.	Hematemesis and melena	2 days	7 days	Gastroenterostomy with peptic ulcer of the jejunum; eroded blood vessel; chronic bronchitis and emphysema; arteriosclerosis; cardiac hypertrophy; hypertrophy of the prostate	Repeated bleeding
1939	F	69	1 yr.	Hematemesis	Within 1 day	Within 1 day	Chronic ulcer, 1 by 1 cm., in the stomach near the pylorus; eroded blood vessel; syphilitic aortitis; arteriosclerosis; cardiac hypertrophy; nephrosclerosis	Persistent bleeding and cardiac insufficiency

course of two to five days. They were also so ill that it was difficult to get them to eat or drink anything. Even those who died in five to ten days took little fluid or nourishment. Time after time in the clinical histories of the fatal cases there appears the statement that the patients were so ill that they could neither eat nor drink or that it was difficult to get them to do so. That is the tragic part of it; for these patients, in a still greater measure than those with less severe illness, need all the support which they can get. In my view, therefore, it can be said that in these cases it is not the treatment that has done harm but the lack of it.

Could some of the patients have been saved by operation with a view to hemostasis? Against this it should be pointed out in the first place that it would have been difficult to dissociate these 26 patients from the total number, at any rate before they had become extremely ill or even before they had become almost moribund. Further, a more detailed clinical and postmortem analysis of the 26 patients shows that practically all of them would have been bad subjects for a resection operation. On admission to the hospital all were suffering from a severe state of shock and debility and some were moribund. Half of them were over 60 years of age, and the oldest was over 83. In many there were complicating diseases, e. g., arteriosclerosis, cardiac fibrosis or renal sclerosis. Many had large ulcers penetrating to the pancreas or liver; extensive resections would have been necessary. In 6 the cause of death was something other than hemorrhage. In actual fact there were only a few for whom, seen in review, one felt that there might have been a reasonable chance that they would tolerate resection. My own view up to now has been that a patient with bleeding gastric ulcer should not be transferred for operation during or just after a hemorrhage, and perusal of the fatal cases in my own material has rather served to strengthen me in this opinion even if I admit that there might be a few cases in which operation might be lifesaving. A gross mortality of 2.5 per cent and a net mortality of 1.5 per cent seem to be satisfactory under the conditions. There must always be a certain basal mortality.

Yet it is not impossible that these figures could be reduced still further. Modern surgery teaches how enormously the prognosis in a number of operations has been improved by the introduction of systematic control of the patient's hemoglobin, plasma protein and water and electrolyte balance, with the readjustment of any deficit by means of blood transfusions and the parenteral administration of dried serum, dextrose solution and isotonic solution of sodium chloride or isotonic solution of bicarbonate before or, particularly, after the operation. There is no doubt in my mind that patients with bleeding gastric ulcer should be on a par with patients operated on; they are suffering from post-

Hemorrhage and cerebral thrombosis, with complete hemiplegia, were thought to be equally responsible for 1 death.

In 19 cases the hemorrhage itself was regarded as the immediate cause of death. In about half these it was thought that there had been persistent hemorrhage and in the other half repeated hemorrhage. In this decision, the length of time which had elapsed since the onset of the bleeding and the question of whether there had been clinical signs

TABLE 3.—*Interval Between Onset of Bleeding and Occurrence of Death*

DAYS.....	0 to 2	2 to 5	5 to 10	Over 10
Number of patients.....	5	8	8	5

TABLE 4.—*Interval Between Admission to Hospital and Occurrence of Death*

DAYS.....	0 to 2	2 to 5	5 to 10	Over 10
Number of patients.....	5	8	8	5

TABLE 5.—*Location of the Ulcers in the Twenty-Six Fatal Cases*

Locus	Number
Stomach.....	9
Pylorus.....	2
Duodenum.....	11
Stomach and duodenum.....	1
Gastroenterostomy opening.....	3

TABLE 6.—*Immediate Cause of Death in the Twenty-Six Fatal Cases*

Embolus of the pulmonary artery.....	2
Perforation and peritonitis.....	2
Bleeding and perforation.....	1
Bleeding and pleuropneumonia.....	1
Bleeding and thrombosis (hemorrhage ?) of the brain.....	1
Persistent bleeding.....	9
Repeated bleeding.....	10

of a fresh hemorrhage were taken into consideration. It must be admitted that it was frequently difficult to distinguish between persistent and repeated hemorrhage.

It was apparent that a number of factors had lessened the patients' capacity for resistance. Nine were over 70 years of age and exhibited, more or less, the general weakness associated with old age. Arteriosclerosis was present in 12 and fibrosis of the myocardium in 10. One had syphilitic aortitis, 1 syphilitic aortitis and aortic aneurysm, 1 chronic purulent bronchitis and emphysema, 1 a small pulmonary abscess, 5

EPIDEMIOLOGIC STUDY OF SEVEN HUNDRED AND FIFTY-SEVEN CASES OF RHEUMATIC FEVER

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DURING World War II rheumatic fever was one of the major causes of lost man days due to sickness in the Navy and Marine Corps. Coincident with large epidemics of hemolytic streptococcus infections which occurred in all the large naval training centers during the years 1942 to 1945 inclusive, the incidence of rheumatic fever rose to epidemic proportions by 1943 and the incidence of valvular heart disease increased accordingly. The number of cases of rheumatic fever in the Navy rose from 148 in 1940 to 7,668 in 1944. The rate per thousand persons increased during the same period from 0.73 to 2.29. The magnitude of the problem of rheumatic fever necessitated the establishment of two naval hospitals for the care of patients with this disease. Likewise, the Army experienced epidemics of hemolytic streptococcus infections as well as a sharp increase in the rate of rheumatic fever. However, the rate of rheumatic fever in the Army was much lower than that in the Navy. Table 1 gives a comparative picture of the rates of rheumatic fever in the Army and Navy and the total number of cases. Table 2 shows that the number of sick days from rheumatic fever in the Navy rose from 12,903 in 1940 to 1,307,475 in 1944. Table 3 points out a similar increase for diseases of the mitral valve from 1940 to 1944.

Rheumatic fever was not among the first ten causes of sick days in the Navy in 1940, but by 1944 it had risen to second place, outnumbered only by simple fractures. Table 4 shows the diseases and noncombat injuries responsible for the greatest number of lost man days in the Navy and Marine Corps from 1940 to 1945.

It is interesting to note that the rate of incidence of rheumatic fever for both the Army and the Navy is considerably less for World War II than for World War I. Most of the cases of rheumatic fever occurred, however, in the training centers, and here the rate far exceeded that

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This work was done while the author was on active duty as an officer in the United States Naval Reserve.

The Bureau of Medicine and Surgery does not necessarily endorse the views and opinions expressed in this article.

This therefore means that hematemesis indicates a worse prognosis than melena. The presence of hematemesis does not depend so much on the site of the ulcer as on the fact that the more sudden and profuse the hemorrhage the greater is the probability that it will manifest itself as hematemesis (Pedersen¹¹). In conformity with this statement, in nearly all the fatal cases in which the bleeding was considered to be the immediate cause of death large eroded vessels were seen at the postmortem examination.

That hematemesis indicates a worse prognosis than melena is also found with other forms of treatment. Thus Hansen (cited by Pedersen¹¹) in a collected material of 97 fatal cases of bleeding peptic ulcer from the Municipal Hospital of Copenhagen during the period 1915 to 1935, found that in 85 the hemorrhage had manifested itself as hematemesis.

At the autopsies, nine gastric as compared with eleven duodenal ulcers were found. This is a greater number of gastric ulcers than that which occurs in the clinical material. Thus Alsted found about five times as many duodenal as gastric ulcers. The gastric ulcers clearly had a greater tendency to fatal hemorrhage.

In settling what shall be regarded as gross mortality and what is net mortality, one can naturally establish different criteria. In calculating my gross mortality of 2.5 per cent, I have included all the deaths if they occurred while the patients were in hospital. In calculating my net mortality of 1.5 per cent, I have excluded deaths due to causes other than hemorrhage and deaths which occurred so soon that the patients had not received the treatment. The justification for excluding the latter can of course be contested, but with a view to comparison I have proceeded on the same lines as Miller and others,¹² by which they obtained the figures 4 per cent and 1.9 per cent¹ for gross and net mortality respectively.

Although it may now be said to have been proved that the free feeding program gives lower mortality figures and although Miller¹³ in my opinion expresses it accurately when he says that "to the average case the prompt feeding program offers the best chance for survival," it may nevertheless be in order to inquire whether the treatment in the fatal cases has not only been useless but has even done harm.

It must be pointed out to begin with that in a large number of the fatal cases the patients did not get any treatment at all. Thus 5 patients died shortly after their admission to the hospital, and they moreover were so ill that they could neither eat nor drink. Eight died in the

11. Pedersen, J.: *Nord. med.* **9**:252, 1941.

12. Nicholson and Miller.³ Rasberry and Miller.⁴

13. Miller, T. G.: *Ann. Int. Med.* **15**:390, 1941.

ence with this disease, it is considered of value to report a study of the epidemiologic pattern in rheumatic fever in a group of enlisted personnel in the Navy and Marine Corps in order to add to the general fund of information of factors which set the stage for this disease.

DESCRIPTION OF STUDY GROUP AND METHODS

The patients under consideration in this study were admitted to the United States Naval Hospital at Dublin, Ga., between March 15, 1945 and March 15, 1946. There were 1,470 patients admitted for rheumatic fever during this period, and 757 of these patients, all enlisted

TABLE 3.—*Incidence of All Diseases of the Mitral Valve in the Navy and Marine Corps in 1940 to 1944*

Year	Number of Cases	Days of Sickness
1940.....	60	3,677
1941.....	306	14,538
1942.....	775	31,203
1943.....	1,991	85,153
1944.....	1,856	122,440

TABLE 4.—*Diseases and Noncombat Injuries Responsible for the Greatest Number of Lost Man Days in the Navy and Marine Corps in 1940 to 1944 **

Year	Greatest Amount of Lost Time	Per Cent of Total	Next Greatest Amount of Lost Time	Per Cent of Total	Third Greatest Amount of Lost Time	Per Cent of Total
1940	Catarrhal fever, acute	8.89	Gonococcic infection, urethra	8.62	Appendicitis, acute	3.51
1941	Catarrhal fever, acute	7.55	Gonococcic infection, urethra	4.30	Appendicitis, acute	3.47
1942	Catarrhal fever, acute	8.67	Gonococcic infection, urethra	3.89	Appendicitis, acute	3.37
1943	Malaria, all forms	8.48	Gonococcic infection, urethra	6.05	Fracture, simple	3.96
1944	Fracture, simple	4.07	Rheumatic fever	3.68	Catarrhal fever, acute	3.43

* The data in this table are taken from the medical statistics of the United States Navy. The percentages are based on the total days of sickness for all diseases and noncombat injuries.

male personnel of the Navy and Marine Corps, comprise the study group. The hospital is one of two established by the Navy as centers for the treatment of rheumatic fever, and patients were transferred to it principally from other naval hospitals east of the Mississippi River.

The majority of the patients were interviewed for this study after they had been in the hospital at least two months.

OBSERVATIONS

1. *Location of the Patient's Home and the Number and Per Cent by States Who Had Rheumatic Fever Before Enlistment.*—The community in which the patient had lived during his childhood and early adulthood

hemorrhagic shock, and much risk can be obviated by making good, as far as possible, the deficit of hemoglobin, plasma protein, water and salts which exists. This is one of the things which the free feeding program aims at through the liberal supply of food and drink. When I now reflect on my fatal cases, I admit that I employed blood transfusion on far too small a scale, and from now on I shall arrange for the systematic control of cases which threaten to terminate fatally as well as for the more ample use of blood transfusions. According to investigations from Witt's clinic by Black and Smith,¹⁴ the use of dried serum cannot be advised as it compares unfavorably with whole blood and may have ill effects.

If in the future I should consider the advisability of operation, it shall be, as seen from the perusal of my fatal cases, in instances in which the patient is more than 40 years of age, has persistent or repeated bleeding, manifesting itself as hematemesis, and threatens to die in spite of repeated blood transfusions. There should be no serious contraindications to operation, the presence of an ulcer should have been proved by roentgenologic study and a good surgeon should be available.

SUMMARY

1. Results are reported from fifteen years of the systematic use of free feeding in bleeding peptic ulcer, with special regard to mortality.
2. The treatment has been used as a routine measure in a total of 1,031 consecutive cases of bleeding peptic ulcer.
3. Of the 1,031 cases, 26 terminated fatally during the patient's stay in the hospital.
4. In all the fatal cases except 1 the patients were more than 40 years old. Many had large ulcers penetrating to the pancreas or the liver, and many had complicating diseases.
5. If all the fatal cases are included, the gross mortality is 2.5 per cent. If cases are excluded in which death was entirely or mainly due to causes other than bleeding as well as those in which the patients died twenty-four hours after admission to the hospital and therefore before they had received the treatment, the net mortality is 1.5 per cent.
6. A more ample use of blood transfusions is recommended in cases which threaten to terminate fatally.

14. Black, D. A. K., and Smith, A. F.: *Brit. M. J.* 1:187, 1941.

(24.5) had rheumatic fever prior to enlistment. The comparatively large numbers of men with previous rheumatic fever who came from homes in the New England, Middle Atlantic, North Central and South Atlantic states indicate that the disease is widespread in these sections. The high per cent of men from Florida, Georgia, Mississippi and North and South Carolina who had the disease in childhood is no index of the true incidence of rheumatic fever in these states but does lend weight to the idea that the disease is not uncommon in these areas. A recent investigation of the incidence of rheumatic fever in school children in Dublin, Ga., bears out this observation.⁴

2. *Age at Onset of Rheumatic Fever.*—The age of the patient at the time of his first recognized attack of rheumatic fever and the number of patients who apparently acquired the disease at this age are shown in

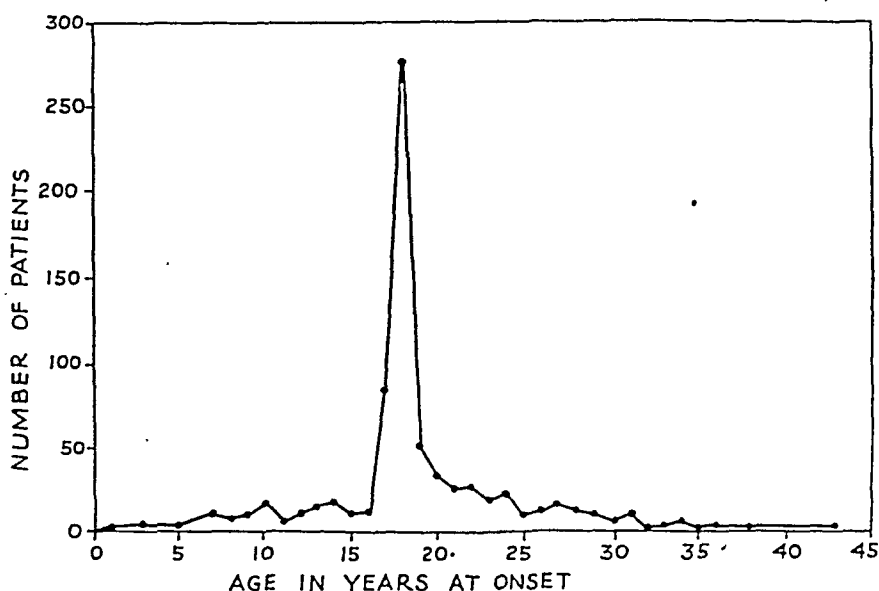


Fig. 1.—Age of patients at the time of the onset of rheumatic fever.

figure 1. The youngest age at the time of onset was 1 year, and the oldest was 43. Seven patients had their first attack of rheumatic fever between the ages of 1 and 5 inclusive, 50 between the ages of 5 and 10, 69 between the ages of 11 and 16 and 412 between the ages of 17 and 19 inclusive. Seventeen is the minimum age for enlistment in the Navy and Marine Corps. The onset occurred in 139 patients when they were between the ages of 20 to 26 inclusive, and in 55 the disease made its initial appearance when they were between 26 and 30. Twenty-five had rheumatic fever for the first time between the ages of 31 and 43 inclusive.

A percentage analysis of figure 1 reveals that 0.9 per cent of the total group of 757 acquired rheumatic fever between the ages of 1 and

4. Quinn, R. W.: The Incidence of Rheumatic Fever and Heart Disease in School Children in Dublin, Georgia, *Am. Heart J.* **32**:234 (Aug.) 1946.

for the Navy as a whole, although exact figures are not available. Also it is highly probable that the rate for the training centers exceeded that for the civilian population.

Although of no epidemiologic importance, it seems worth while to comment that the final chapter in the illness of the men who acquired rheumatic fever in the armed forces has not been written; they have many days of sickness ahead of them. From the studies of Jones and Bland¹ and Hedley² it can be predicted that many of these men will have impaired ability for activity and that the life expectancy of the

TABLE 1.—*Number of Cases of Rheumatic Fever and Rate per Thousand in the Army and Navy for World War I and World War II**

Year	Number of Cases		Rate per 1,000	
	Army	Navy	Army	Navy
1917.....	5,423	1,057	7.99	4.30
1918.....	18,020	2,772	7.16	5.50
1919.....	1,923	1.91
1940.....	122	148	0.36	0.73
1941.....	1,113	489	0.83	1.40
1942.....	1,649	868	0.51	1.04
1943.....	7,426	5,808	1.08	2.75
1944.....	5,731	7,668	0.72	2.29
1945.....	3,675	6,461	0.52	1.76

* The Surgeon General's report (Army) for the period of World War I, April 1, 1917 to Dec. 30, 1919 inclusive, gives for acute articular rheumatism a total of 24,770 cases, with an incidence rate of 6.00 per thousand persons per annum. The incidence of rheumatic fever (Army) in each year of the period 1941 to 1945 is considerably in excess of that in the Army's prewar experience. For several years immediately preceding the war the rate varied between 0.8 and 0.36 per thousand per annum.

TABLE 2.—*Rheumatic Fever in the Navy and Marine Corps in 1940 to 1945*

Year	Number of Cases	Days of Sickness
1940.....	148	12,903
1941.....	489	35,215
1942.....	868	62,952
1943.....	5,808	472,703
1944.....	7,668	1,307,475
1945.....	6,461	1,245,380

group as a whole will be shortened. Seventy-five (21.5 per cent) of 349 patients included in this group and studied separately by Lt. Comdr. T. W. Steege already had valvular heart disease at the time of discharge.³

Rheumatic fever is of extreme importance as a world health problem, and few facts are known concerning its epidemiology, etiology and pathogenesis. Because of the Navy Medical Corps's wide experi-

1. Jones, T. D., and Bland, E. F., Jr.: Rheumatic Fever and Heart Disease: Completed Ten-Year Observation on 1,000 Patients, *Tr. A. Am. Physicians* **57**:267, 1942.

2. Hedley, O. F.: Mortality from Rheumatic Heart Disease in Philadelphia During 1936, *Pub. Health Rep.* **52**:1907 (Dec. 31) 1937.

3. Steege, T. W.: Unpublished data.

the cases under study the disease apparently made its initial appearance after the men had reached young adulthood. This of course gives a considerably different picture from that given by the statistics on age at first attack of rheumatic fever gathered in hospital clinics. It is well known that there are many persons with valvular heart disease who give no past history of rheumatic fever, perhaps 40 per cent; also it is possible that some of these patients actually did have rheumatic fever in childhood which was unrecognized. This present study emphasizes further that under conditions which exist in the Navy training centers rheumatic fever becomes a disease of young adults.

4. *Number of Attacks of Rheumatic Fever per Patient Before and After Enlistment.*—One hundred and eighty-five patients (24.5 per

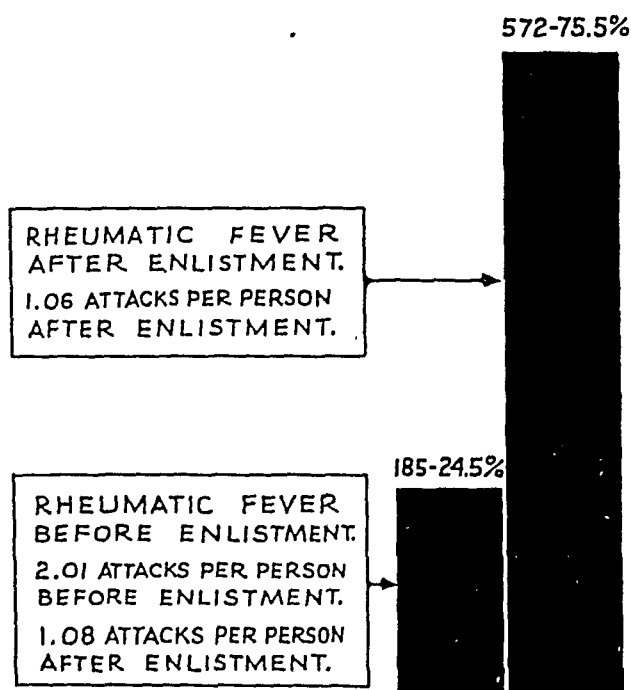


Fig. 3.—Number of attacks of rheumatic fever per patient before and after enlistment.

cent) gave a definite history of rheumatic fever before enlistment in the Navy or Marine Corps. The total number of previous attacks in these patients was 373 (2.01 attacks per person). The number of previous attacks per person varied widely, 105 having had one attack and 1 patient estimating that he had experienced fifteen separate bouts before enlistment.

Five hundred and seventy-two patients (75.5 per cent) had never had rheumatic fever prior to enlistment in the Navy or Marine Corps. Of this number, 538 had one attack, 21 had two attacks, 4 had three attacks and 1 had four attacks after enlistment. These data are given in figure 3.

coincided in at least 95 per cent of the cases. The majority of patients came from homes east of the Mississippi River and were stationed in this same area at the time of the onset of their present illness.

The number who were known to have had rheumatic fever prior to enlistment was determined by a careful taking of the history, and by the time the patients were interviewed a past history of rheumatic fever had been established or ruled out. Furthermore, it was the policy of the medical survey board at the hospital to discharge all persons from the service who had had more than one attack of rheumatic fever. The validity of the first attack was considered carefully by the survey board, and in most cases a letter from the patient's family physician gave further proof of earlier illness. The patient was not considered to have had a previous attack of rheumatic fever unless there was clearcut supporting evidence.

In table 5 the home states of 754 of the patients are grouped according

TABLE 5.—*Location of Home of Patients with Rheumatic Fever*

Geographic Area, States	Number of Patients	Number with Rheumatic Fever Before Enlistment	Per Cent with Rheumatic Fever Before Enlistment
New England.....	87	21	24.1
Middle Atlantic.....	197	56	28.4
South Atlantic.....	160	42	26.2
South Central.....	77	10	12.9
North Central.....	211	51	24.1
Plateau.....	8	1	12.5
Pacific.....	14	4	28.5

to geographic areas. The North Central states contributed the highest number, 211 men, and of this number 51 (24.1 per cent) gave a history of rheumatic fever prior to enlistment. In the Middle Atlantic states there were 197, with 56 (28.4 per cent) giving a history of previous rheumatic fever. In the South Atlantic states there were 160, with 42 (26.2 per cent) having had the disease before. In the New England states the corresponding figures were 87 and 21 (24.1 per cent); from the South Central states there were 77, of whom 10 (12.9 per cent) had had previous rheumatic fever, and from the Pacific states there were 14, 4 of them (28.5 per cent) with a past history of the disease. The smallest group, 8, were from the plateau states, and only 1 of these (12.5 per cent) had a history of previous rheumatic fever.

Exact figures were not determined for the entire group, but at least 75 per cent came from urban homes.

Comment: It is not intended that these figures should give any estimate of the incidence of rheumatic fever in the respective geographic areas; they merely indicate that the disease is present in all these regions. A majority of patients grew up in urban areas, and a large per cent

mate, seaman or fireman, and 96 were in outgoing units, awaiting transfer to a station for new duty. Approximately three-fourths of this group had just completed boot training. Their duties consisted mainly in deck, cleaning, "head" and galley details.

All patients who became ill on a foreign shore had duties of rated or nonrated personnel, and there was nothing unusual, from an epidemiologic standpoint, about their work. Patients who became ill while on sea duty, either in port or at sea, were for the most part members of a ship's company. Their duties were those of any enlisted personnel,

TABLE 6.—*Geographic Location and Duty Status of Patients at the Time of Onset of Rheumatic Fever in the Service*

Location	General Duty	Outgoing Unit	Boot Training	Service School	Total
Continental United States.....	101	96	274	160	631
Foreign shore duty					
North Africa.....	6	6
England.....	3	2	5
Pacific area.....	20	2	22
Total.....	29	4	33
Sea duty in port					
United States.....	27	27
England.....	2	2
Pacific.....	7	7
Mediterranean.....	2	2
France.....	1	1
North Africa.....	1	1
Total.....	40	40
Sea duty at sea					
Atlantic.....	19	19
Pacific.....	31	31
Panama Canal.....	2	2
Gulf of Mexico.....	1	1
Total.....	53	53
Totals.....	223	100	274	160	757

such as those of the signalman, deck hand or fire control man, but the majority were nonrated men.

Comment: The prevalence of rheumatic fever in the Navy and Marine Corps as a whole is not high. This suggests that the Navy and Marine Corps provide healthy occupations as far as rheumatic fever is concerned. However, in war years epidemics of rheumatic fever occur. The highest rate is found in the recruit training centers and service schools of the Navy. These establishments were located in New York, Rhode Island, Maryland, Illinois and Idaho, where annual death rates from rheumatic fever in white persons aged 5 to 24 years for the years 1939 to 1941 were extremely high.⁵ This suggests that the sections where training centers and service schools are located favor a high rate of rheumatic fever. In a small number of cases the disease appeared in men while in tropical or subtropical zones.

5 inclusive, 6.6 per cent between 5 and 10, 9.1 per cent between 10 and 16, 54.4 per cent between 17 and 19, 18.4 per cent between 20 and 25, 7.3 per cent between 25 and 30 and 3.3 per cent between 31 and 43.

3. *Ages of Patients Comprising the Study Group.*—The Patients' ages ranged from 17 to 43 (fig. 2). As might be expected, the youngest age groups accounted for the majority of patients, 460 (61.1 per cent) being from 17 to 19. The largest number of patients, 279 (36.9 per cent), were 18 years of age. The number of patients decreased

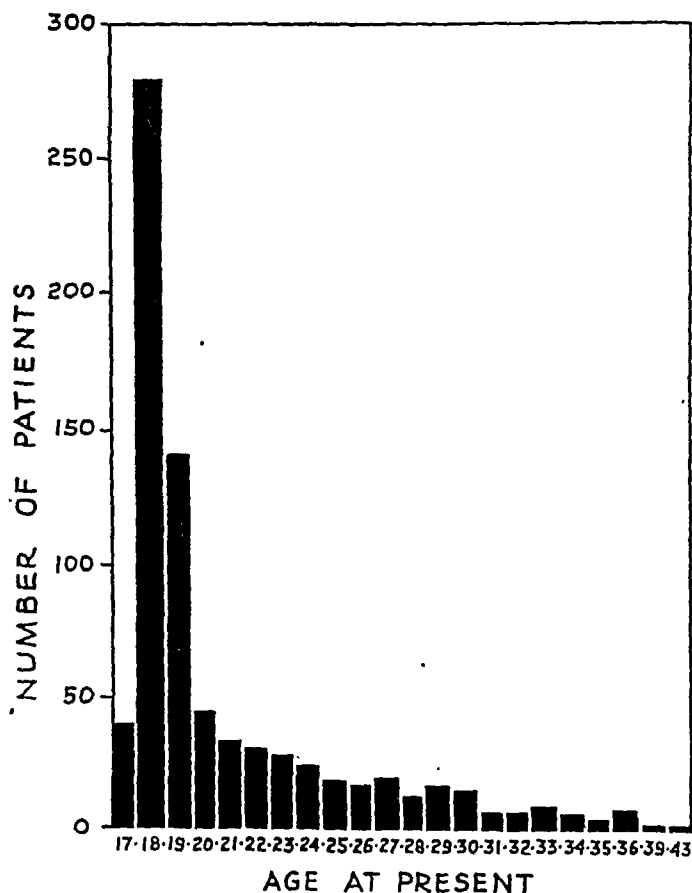


Fig. 2.—Age of the patients in the study group.

gradually in the older age groups; there were 45 who were 20 years of age and only 1 each at the age of 39 and 43.

Comment: The age at the first attack of rheumatic fever in the largest number of this group is considerably older (17 to 19) than the age of onset for persons in the civilian population as a whole (7 to 10).⁵ One point of view in relation to rheumatic fever is that it practically always has its onset in childhood, but in the majority of

5. Armstrong, D. B., and Wheatley, G. M.: *Studies in Rheumatic Fever*, Metropolitan Life Insurance Company, November 1944.

Even more significant is the fact that 79.6 per cent of the group who acquired the disease in their first year in the Navy became ill within the first six months. However, in the light of past experience this course of events might have been expected. Massing of troops has always been attended by an increase in the incidence of disease,⁸ and it has been said that the first months of life in the armed services are as dangerous to the recruit, from the standpoint of disease, as the first years of life for the infant.⁹ On the other hand, only a small number of seasoned men were stationed at training centers or service schools, and for this reason it can only be guessed what would have happened to older seasoned men in circumstances similar to those affecting trainees.

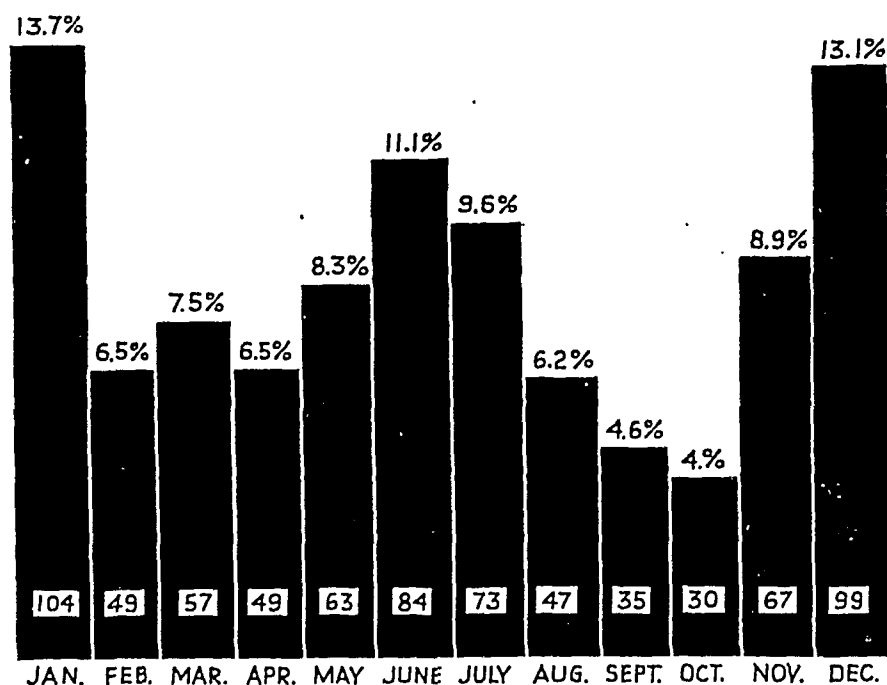


Fig. 5.—Month of onset of rheumatic fever and number and per cent of patients who acquired rheumatic fever in each month.

7. *Month of Onset of Present Illness.*—Figure 5 shows the number and per cent of the total group who became ill each month. (It is self explanatory and needs no particular description.)

Comment: The figure is not meant to give a picture of the seasonal trend of rheumatic fever in the Navy. It merely illustrates the fact that rheumatic fever can and did occur at any season.

8. *Types of Infection Which Preceded the Onset of Rheumatic Fever.*—The types of infection which preceded the onset of rheumatic fever are listed in table 7. Five hundred and forty-five patients (71.9 per

8. Hale, R. A.: *Epidemiology in Mobilization*, Mil. Surgeon **82**:243 (March) 1938.

9. Boudreau, F. G.: *Epidemic Hazards in War*, New York State J. Med. **40**:1089 (July 15) 1940.

The 572 patients who did not have the disease before enlistment had a total of six hundred and twelve attacks (1.06 attacks per person) after enlistment, whereas the 185 with previous rheumatic fever had two hundred attacks (1.08 attacks per person) after enlistment. A total of eight hundred and twelve attacks of rheumatic fever after enlistment occurred in the study group (1.07 attacks per person).

Comment: One fourth of the patients had rheumatic fever prior to enlistment. This figure is smaller than that found by Manchester in his study of rheumatic fever in naval personnel.⁶

The number of attacks per person after enlistment was approximately the same for patients with as for those without previous experience with rheumatic fever. Possibly those who acquired rheumatic fever in the Navy are just as susceptible to the disease as the group who had it previously when conditions favoring its onset are present.

5. *Geographic Location and Duty Status of Patients at the Time of Onset of Illness.*—Geographic Location (table 6): Six hundred and thirty-one men had their present attack of rheumatic fever within the continental limits of the United States. The great majority (531 or 70 per cent) acquired their illness in five states, Illinois, Maryland, New York, Rhode Island and Virginia. Large numbers of men were stationed in these states. Boot camps and service schools were located at Sampson, N. Y., Bainbridge, Md., and Great Lakes, Ill. A construction battalion training camp was located in Rhode Island, and many service schools and naval establishments were in the vicinity of Norfolk, Va. Thirty-three men were on foreign shore duty when their illness began, 6 being in North Africa, 5 in England and 22 in the Pacific area, which included the territory of Hawaii and the South-West and Central Pacific. Ninety-three became ill while on sea duty, 40 while their ship was in port and 53 while at sea. Of the 40 whose illness began in port, 27 were in United States ports, chiefly along the east coast in New York, Boston and Norfolk, 2 were in England, 7 were in Pacific ports (not in the United States), 2 were in Mediterranean ports, 1 was in a North African port and 1 was in Normandy, France. Nineteen of those stricken at sea were in the Atlantic (17 in the North Atlantic), 32 were in the Pacific (at least 27 in the South West Pacific), 2 were in the Panama Canal Zone and 1 was in the Gulf of Mexico.

Duty Status (table 6): The duties of those who became ill within the continental limits of the United States can be divided into four classes: Two hundred and seventy-four were in boot training; 160 were in service schools such as gunnery or radar schools or schools for radio technicians; 101 were on general duty, which included any of the duties of the rated or nonrated men such as the boatswain's mate, pharmacist's

6. Manchester, R. C.: Rheumatic Fever in Naval Personnel, *Arch. Int. Med.* 66:317 (March) 1946.

were many thousands of cases of laryngitis, sinusitis and rhinitis in which the condition was undoubtedly caused by this organism.

In the present study group 76 patients (10 per cent) had no infection of the upper respiratory tract preceding their rheumatic fever of which they had been aware. An important observation in this regard was noted by Lt. Comdr. James B. Black, who examined many patients with acute rheumatic fever at the onset of their illness. When questioned, patients frequently stated that they had no sore throat, but examination often revealed unmistakable evidence of pharyngitis.¹⁰

Eleven patients were not questioned concerning preceding infection.

Comment: It has been noted for many years by various observers that a close relationship exists between rheumatic fever and a preexisting

TABLE 8.—*Incidence and Rates per Thousand of Various Diseases in the Navy and Marine Corps*

Diagnosis	Incidence					
	1940	1941	1942	1943	1944	1945
Catarrhal fever.....	27,312	34,050	103,269	281,826	246,037	286,403
Rate per 1,000.....	134.80	97.59	123.73	133.67	73.45	77.96
Scarlet fever.....	25	419	1,348	14,041	16,954	27,117
Rate per 1,000.....	0.12	1.20	1.62	6.66	5.06	7.38
Tonsillitis, acute.....	4,286	7,160	18,597	55,165	72,719	72,047
Rate per 1,000.....	20.96	20.52	22.28	26.16	21.71	19.61
Pharyngitis, acute.....	619	1,229	6,362	26,078	36,744	46,722
Rate per 1,000.....	3.06	3.52	7.62	12.37	10.97	12.72
Rheumatic fever.....	140	489	868	5,808	7,668	6,461
Rate per 1,000.....	0.73	1.40	1.04	2.75	2.29	1.76
Average strength.....	202,614	348,926	834,639	2,108,379	3,349,798	3,673,855

infection of the upper respiratory tract.¹¹ The exact nature of this relationship still is not known, and there are those who believe that streptococci play no part in the pathogenesis of rheumatic fever. Pos-

10. Black, J. B.: Personal communication to the author.

11. Coburn, A. F.: Epidemiology of Streptococcus Hemolyticus Infections at Naval Training Stations, U. S. Nav. M. Bull. **41**:1012 (July) 1943. Wheeler, S. M., and Jones, T. D.: Factors in the Control of the Spread of Acute Respiratory Infections with Reference to Streptococcal Illness and Acute Rheumatic Fever, Am. J. M. Sc. **209**:58 (Jan.) 1945. Packard, F. A.: Philadelphia M. J., April 21 and April 28, 1900. Thomson, St.C.: Rheumatic Fever in Relation to the Throat, Practitioner **66**:35, 1901. Kalbak, K.: Undersøgeleser over O-streptolysin og. forekomsten af O-antistreptolysin I serum, Copenhagen, Ejnar Munksgaards forlag, 1942 (English summary). Bruun, E.: Experimental Investigations in Serum Allergy with Reference to the Etiology of Rheumatic Joint Diseases, *ibid.*, 1940. Paul, J. R.: The Epidemiology of Rheumatic Fever and Some of Its Public Health Aspects, ed. 2, New York, Metropolitan Life Insurance Company, 1943.

In general, the duties of the men in the study groups were not different from those of enlisted personnel in the Navy or Marine Corps who did not get rheumatic fever. It cannot be said that the duty status of the patients revealed anything of epidemiologic importance, although it has been stated by some that the strenuous activities of trainees, which are attended by excessive fatigue, make them more susceptible to infectious disease.

6. *Length of Time on Active Duty Before the Onset of Rheumatic Fever.*—Figure 4 shows the number and per cent of patients who acquired rheumatic fever during each three month period after going on active duty. Three hundred and six (40.4 per cent) acquired rheumatic fever during the first three months of active duty. One hundred and

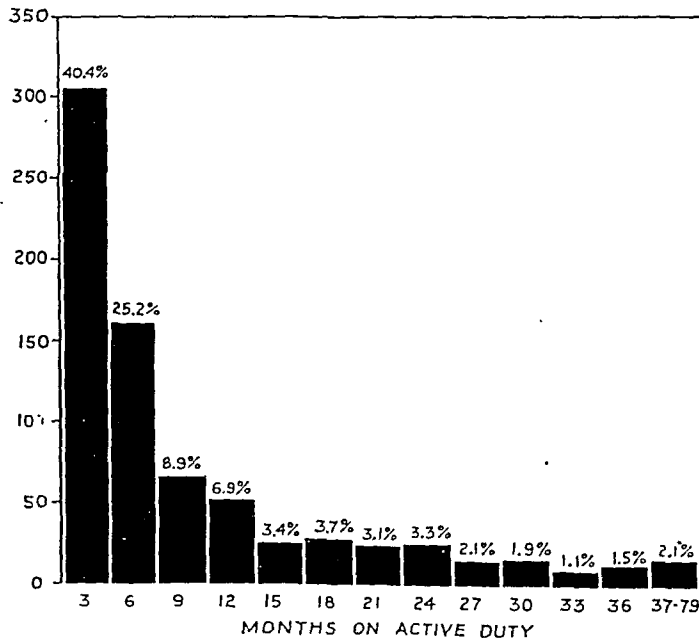


Fig. 4.—Number and per cent of patients who acquired rheumatic fever in each three month period after entry into the navy.

sixty-one became ill during the second three month period. Sixty-seven (8.9 per cent) and 52 (6.9 per cent) became ill during the third and fourth three month periods. A total of 586 (77.4 per cent) acquired rheumatic fever during their first year in the Navy, 103 (13.6 per cent) during the second year, 52 (6.9 per cent) during the third year and only 16 (2.1 per cent) from the thirty-seventh to the ninety-seventh month inclusive.

Comment: It is significant that 77.4 per cent of the men acquired rheumatic fever during the first year of their "Navy life." This number is remarkably close to the observations of Manchester⁶ and Coburn.⁷

7. Coburn, A. F.: The Management of Navy Personnel with Rheumatic Fever, U. S. Nav. M. Bull. 41:1324 (Sept.) 1943.

indefinitely. Greenwood and Topely studied communities of mice for more than ten years, and they did not find any important exception to the rule that an infected herd receiving unselected healthy immigrants will never clear itself of the infectious disease.¹³

During the early months of the war the period of training was from ten to twelve weeks, but later, as the manpower shortage became more acute, the time was shortened to six weeks. The men were housed in two deck barracks, one company to each deck. They slept in double-decked bunks and sometimes triple-decked bunks. The space between the bunks was about 3 feet (91.4 cm.) and less if more than 130 men were housed in a barracks. Mess took place in large halls with galley and scullery facilities for many companies. Recreational facilities, such as the movies and ship's service, were used by everyone at the training center. Swimming pools were used by a large number of different companies.

Sick call was held three times a day at dispensaries, each serving a number of different companies. The sick calls were large and crowded. Patients requiring hospitalization were admitted to dispensaries or naval hospitals located at the training centers. Because of the shortage of beds in the hospital during the epidemic of hemolytic streptococcus infections and because of other reasons, isolation of patients was not carried out. Frequently, men were ill and would not report to "sick call" for several days because they did not want to miss some phase of their training or a liberty or "boot" leave. Often when hospitalized they were sent back to duty before they were completely well, sometimes knowingly by the medical officer and other times innocently. The acute need for beds and the constant pressure and pleadings of patients to get out of the hospital occasionally broke down the firmest resistance of the medical officers. If a man missed too much of his training because of illness, he was not sent back to his old company but to a new one. Frequently the men who had complications from a hemolytic streptococcus infection were sent to new companies.

The decks of the barracks were swept dry twice daily and then swabbed. The wards of the hospital likewise were swept dry, and at least once a week they were buffed with an electric buffer. Frequently a visible cloud of dust rose from the buffer or sweeper. There was no opportunity to leave barracks empty or to clean them thoroughly after a company had completed training. The speeded up training program required every available barracks as soon as it was emptied. Bedding was issued newly to each incoming company, but there was no opportunity for airing or washing bedding during the winter months.

13. Greenwood, M.: The Preventive Aspects of Medicine, *Lancet* 1:201 (Jan. 27) 1934.

cent) had a definite infection of the upper respiratory tract preceding the onset of the rheumatic syndrome. The clinical diagnoses given to these infections were in the following order of frequency: catarrhal fever, tonsillitis, pharyngitis, laryngitis, sinusitis and bronchitis. The term catarrhal fever as used by the Navy does not designate a specific disease but is used to classify nonspecific febrile illnesses of the upper respiratory tract. Undoubtedly, in many cases of hemolytic streptococcus infections the diagnosis of catarrhal fever was made. One hundred and seven (14.1 per cent) of the patients had scarlet fever before their rheumatic fever. Unusual infections or illnesses preceded the rheumatic syndrome in 18 (2.4 per cent) patients. Of this number, 2 had dysentery, 1 appendicitis and 9 pneumonia; 3 had teeth extracted, 1 had an abscess of the finger, 1 had fever of unknown cause and 1 had had cholera immunization prior to his illness. It was difficult to establish accurately the length of time between the onset of the infection of the upper respiratory tract and the onset of symptoms of rheumatic fever, but the extreme limits were around two days and two months. Most of the patients dated the onset of their illness with the beginning of

TABLE 7.—*Type of Infection Which Preceded Rheumatic Fever*

	Number	Per Cent
Infection of the upper respiratory tract (catarrhal fever, tonsillitis, pharyngitis, laryngitis, sinusitis, bronchitis).....	545	71.9
Scarlet fever	107	14.1
Unusual infections or events.....	18	2.4
No preceding infection.....	76	10.0

pain in the joints. A few stated that their sore throat did not start until after they had noticed pain and swelling in the joints. It should be pointed out that rarely was it possible to determine from the record of the patient's health the infecting organism associated with the infection of the upper respiratory tract which preceded the rheumatic syndrome. However, most of the patients were stationed at naval establishments in which hemolytic streptococcus infections were epidemic; also, the clinical manifestations of their respiratory infections were similar to those in patients with known hemolytic streptococcus infections.

In a consideration of the experience of the Navy as a whole, table 8 clearly shows the rise in the rate of rheumatic fever from 1940 through 1943 as infections of the upper respiratory tract and scarlet fever increased. It is impossible to know how many of the infections diagnosed as catarrhal fever actually were hemolytic streptococcus infections; a conservative estimate might be 50 per cent. Acute pharyngitis, acute tonsillitis and scarlet fever probably were all caused by the hemolytic streptococcus. These infections do not represent the total number of streptococcic infections for the years mentioned, because there

coccus infections isolated. This same questionable practice is carried on in civilian life.

It is not within the scope of this study to describe the work of the Navy Epidemiologic Units in studying and attempting to prevent the conditions which were of epidemiologic importance in naval training centers. It also should be pointed out that it is not possible to describe individual variations in the epidemiologic pattern which existed in different training centers; only the general pattern has been discussed.

COMMENT

This study does not pretend to give a picture of the epidemiology of rheumatic fever in the Navy as a whole. What has been said applies only to the 757 patients under consideration. It is evident that when this group of young men, susceptible to rheumatic fever, were introduced into a crowded community in which hemolytic streptococcus infection and rheumatic fever were epidemic they acquired rheumatic fever. It is impossible to know at present all the factors in the individual person or in the community which are of significance in the epidemiology of the disease. However, in relation to this study, it was found that of importance were the factors of intermittent introduction of susceptible recruits into an infected environment, crowding, previous rheumatic fever, preceding infection of the upper respiratory tract, relatively young "Navy age," possibly the strenuous duties of boot training and the location of the boot camps in areas in which the civilian death rate for rheumatic fever was high.

SUMMARY AND CONCLUSIONS

1. A group of 757 enlisted male personnel with rheumatic fever in the United States Navy and Marine Corps were included in an epidemiologic study.

2. The rate of rheumatic fever for the United States Army and Navy increased sharply during both World War I and World War II. Rates in the Navy were as follows: 1940, 0.73; 1931, 1.40; 1942, 2.75; 1943, 2.29, and 1945, 0.52. In the Army there were the following rates: 1940, 0.36; 1941, 0.83; 1942, 0.51; 1943, 1.08; 1944, 0.72, and 1945, 0.52.

3. That 24.5 per cent of the study group had had previously recognized rheumatic fever before enlisting in the Navy or Marine Corps is highly significant. This knowledge suggests that these persons were highly susceptible to rheumatic fever.

4. A majority of patients came from urban homes. The areas which produced the largest numbers and percentages of patients with

sibly the truth lies somewhere between these two views, and a combination of a peculiarly susceptible host plus a hemolytic streptococcus infection is necessary in most cases to produce the disease known as rheumatic fever. The Navy's experience lends support to this hypothesis, but since the etiology and pathogenesis of rheumatic fever are still mysteries, there are few facts to recommend one viewpoint above another.

Twenty-four and five-tenths per cent of the patients had rheumatic fever previously, as compared with an estimated 5 to 20 per thousand in the Navy as a whole who had the disease prior to enlistment.⁶ Eighty-nine per cent of this group had either an infection of the upper respiratory tract or scarlet fever preceding their rheumatic fever. Only 10 per cent gave no history of a preceding infection of the upper respiratory tract.

9. *Environment of Patients at the Time of Onset of Rheumatic Fever.*—A detailed description of the environment of each person at the time of onset of his illness would be time consuming and confusing. Since the highest incidence of rheumatic fever occurred in boot camps and training schools, it will be most profitable to examine these environments in detail. A word about ships will serve to illustrate a point discussed later. Sleeping and mess compartments on ships were generally crowded, but ventilation was usually excellent. Hours of duty were long and at times strenuous. It is always damp at sea, and frequently men stood long watches in wet clothing, exposed to the elements at their worst. Yet the number who acquired rheumatic fever at sea is small when compared to the total. Another point worth noting is that streptococcic infections are uncommon when a ship has been at sea for more than a few days.

The methods of housing, feeding, and training naval recruits have been described by others,¹² but some of their observations bear repetition because of their importance in the epidemiology of rheumatic fever. Recruits were formed into companies of from 120 to 130, and occasionally the companies numbered 140. New companies were inducted every few days, and their training programs were staggered. They were trained as separate units, but there was ample opportunity for mixing of the companies. In this manner a continuous stream of susceptible persons was introduced into an infected environment. There is much experimental evidence that if an infectious disease is set going in a community and recruits susceptible to the disease are continually introduced into that community, then the disease will persist

12. Schwentker, F. F.; Hodes, H. L.; Kingland, L. C.; Chenoweth, B. M., and Peck, J. L.: Streptococcal Infection in a Naval Training Station, *Am. J. Pub. Health* 33:1455 (Dec.) 1943. Coburn, A. F.: The Control of Streptococcus Hemolyticus, *Mil. Surgeon* 96:17 (Jan.) 1946.

14. This study adds further evidence that hemolytic streptococcus infection plays a part in the pathogenesis of rheumatic fever.

15. The staggered introduction of fresh recruits and the high degree of crowding of both infected and susceptible persons in semiclosed spaces with inadequate ventilation from an epidemiologic standpoint, plus a constant secondary reservoir of infective material in bedding and floor dust, favored the development of epidemics of hemolytic streptococcus infections followed by an epidemic of rheumatic fever.

Captain F. R. Lang, of the Medical Corps of the United States Navy, Chief of the Medical Statistics Division, Bureau of Medicine and Surgery, Navy Department, and Eugene L. Hamilton, Director, Medical Statistics Division, Office of the Surgeon General, War Department, supplied valuable data used in making tables 1, 2, 3, 4 and 7.

One central heating unit served each barracks, but seldom did it heat the entire building. As a result the barracks were kept closed as tightly as possible during the winter months, and although adequate ventilation for comfort usually was maintained, conditions were poor from the standpoint of epidemiologic control. Often the opposite state of affairs was true on a ship. During cold weather, men gathered indoors in crowds. Seven hundred and seven (93.4 per cent) of the patients comprising the study group were living in crowded conditions at the onset of their illness. Crowding is not easy to define, but by any standard of adequate housing navy barracks are crowded when filled to capacity.

The great navy recruit training centers were located at Sampson, N. Y., Great Lakes, Ill., Bainbridge, Md., and Farragut, Ida. The weather in these areas is characterized by hot summers and cold winters, with snow and rain in abundance. Foul weather, or macro-climate as it is called by Paul,¹⁴ forced the men indoors for their classes and recreation. In this manner a bad micro-climate was created, that is, one which favored the spread of contagious disease. Dampness is difficult to measure, and the role it plays in the pathogenesis of rheumatic fever is not understood; however, 640 patients (85 per cent) considered their environment to be damp when they became ill.

At one time the Navy was faced with a desperate situation wherein epidemics of hemolytic streptococcus infection were a grave menace to the training program. Because of the seriousness of the problem, prophylaxis with sulfonamide compounds was instituted.¹⁵ The incidence of hemolytic streptococcus infections was reduced dramatically, and at the same time the rate of rheumatic fever fell; these reductions, however, were only temporary (table 8). Later, certain strains of hemolytic streptococci acquired resistance to the sulfonamide compounds and the incidence of infection by these organisms returned to epidemic proportions.¹⁶ Similar experiences were observed in other naval and army establishments.

In the Navy, as in civilian life, patients with scarlet fever are isolated or quarantined when facilities for such are available. On the other hand, only in rare instances were patients with hemolytic strepto-

14. Paul, J. R.: Macro-Climate and Micro-Climate in Rheumatic Fever, *Tr. Am. Clin. & Climatol. A.* (1941) **57**:172, 1942.

15. The Prevention of Respiratory Tract Bacterial Infections by Sulfadiazine Prophylaxis in the United States Navy, United States Navy Department, Bureau of Medicine and Surgery, 1944.

16. Sulfadiazine Resistant Strains of Beta Hemolytic Streptococci, *J. A. M. A.* **129**:921 (Dec. 1) 1945. Damrosch, D. S.: Chemoprophylaxis and Sulfonamide Resistant Streptococci, *ibid.* *J. A. M. A.* **130**:124 (Jan. 19) 1946.

Course in the Hospital.—In view of the severe acidosis, an intensive treatment was started. The patient received at once 200 units of regular insulin (of which 100 units were administered intravenously) and 60 units subcutaneously at hourly intervals. During the first fifteen hours, 2,000 cc. of isotonic solution of sodium chloride, 1,000 cc. of a 5 per cent solution of sodium bicarbonate and later 2,000 cc. of a 10 per cent solution of dextrose were administered by intravenous drip. After three hours of treatment, chemical examination of the blood showed no improvement; at this point another 200 units of insulin was administered intravenously and 100 units subcutaneously. Gastric lavage was performed, and black coffee-ground material was removed. From then on the blood sugar level started to fall and the plasma bicarbonate level began to rise. As further measures against signs of impending shock, 500 cc. of whole blood and 250 cc. of plasma were given. To combat the infection, the patient received 30,000 units of penicillin every three hours. The next day at 10 a. m. the condition seemed greatly improved. She had regained consciousness and seemed fairly comfortable. At this time the blood sugar level was 140 mg. per hundred cubic centimeters and the plasma bicarbonate 60 volumes per cent. She had received a total of 1,500 units of regular insulin.

Fifteen hours after initiation of treatment, the patient complained of shortness of breath. At 1 p. m. she was covered with clammy perspiration. The clinical picture for a moment suggested hypoglycemia. Blood was taken for analysis and 50 Gm. of dextrose in 20 per cent solution immediately administered by vein. Thereupon the perspiration ceased, but the general condition deteriorated quickly. At this time the blood sugar value before the administration of dextrose became known. It was 117 mg. per hundred cubic centimeters, and it was obvious that the change in the clinical picture could not be due to hypoglycemia. The situation in the meantime had become alarming. In particular, the following phenomena were observed:

1. The patient complained of shortness of breath. She gasped for breath, and it was noticed that the respiratory movements were performed only with the upper part of the chest. This was carried out by active participation of the auxiliary respiratory muscles; the lower part of the chest remained immobile. At each inspiration the mouth opened and the tongue protruded in a manner seen in succumbing patients. For this reason, we can best describe the respiratory pattern as "agonal breathing."¹
2. The patient showed a generalized muscular weakness. The muscles of the extremities, especially the arms, were distinctly flaccid and hypotonic. The tendon reflexes were still absent.
3. The pulse was irregular. On auscultation we got the impression that this was due to premature beats.
4. The cardiac dullness, which had been normal on the patient's admission to the hospital, was now definitely increased, especially to the left. The apex beat was diffuse and heaving.
5. Over the whole cardiac area a harsh systolic murmur was heard, which had not been there before.
6. The blood pressure, which had fallen during the night to 115 systolic and 65 diastolic, now had risen to 155 systolic and 60 diastolic. The increased pulse pressure manifested itself in a pronounced Corrigan's pulse.

1. Dr. R. F. Loeb, of Presbyterian Hospital, New York, calls this type of respiration "fish mouth breathing." This seems to us an appropriate designation.

rheumatic fever prior to enlistment were the North Central states, the New England states, the South Atlantic states, and the Middle Atlantic states.

5. The age at the time of the first attack of rheumatic fever (17 to 19 inclusive) in the majority of patients was considerably higher than the age at onset for the majority in the civilian population (7 to 10 inclusive).

6. The age range of the patients was from 17 to 43 inclusive. Sixty-one per cent were of the ages 17, 18 and 19. Rheumatic fever occurred more often in patients at the age of 18 than in patients of any other age (279, or 36.9 per cent).

7. The large proportion of men who had a recrudescence of rheumatic fever after enlistment (24.5 per cent) suggests that these persons were especially susceptible to the disease and that factors were present in the new environment which favored reactivation of the rheumatic process.

8. The number of attacks per person after enlistment was the same for those with as for those without previous rheumatic fever.

9. The highest rates of rheumatic fever in the Navy were present in the training centers. The rate for personnel at sea or in foreign shore stations was low. Naval training centers were located in areas in which the death rate for rheumatic fever among civilians was high.

10. In general, the duties of the study group were not different from those of enlisted personnel in the Navy or Marine Corps who did not acquire rheumatic fever.

11. Seventy-seven and two-fifths per cent of the patients acquired their present illness during the first year of their "Navy life." Seventy-nine and three-fifths per cent of these acquired rheumatic fever during their first six months in the Navy.

12. With environmental factors favorable for the development of an epidemic of rheumatic fever and the introduction of susceptible hosts into this environment, rheumatic fever can occur at any season.

13. Seventy-four and two-fifths per cent of the patients had an infection of the upper respiratory tract which preceded the onset of rheumatic fever by an interval of from two to sixty days, with an average of about eighteen days. Laboratory proof that these infections were caused by hemolytic streptococci is lacking. However, the infections occurred in the presence of epidemic hemolytic streptococcus infections, and the clinical characteristics of the two were indistinguishable. Fifteen and three fifths per cent of the patients had scarlet fever preceding rheumatic fever. Ten per cent had no infection of the upper respiratory tract prior to the rheumatic fever.

potassium citrate by mouth, with striking result. In addition to the respiratory paralysis, the author reported the following abnormalities of the electrocardiogram: Before administration of potassium, a severe tachycardia was found. The second and the third lead showed negative P waves, QRS time was prolonged and QRS in lead III slurred; in all three classic leads the S-T segments were depressed and the T waves were low. After the administration of potassium, the cardiac rate slowed down, and a new electrocardiogram showed that the abnormalities had almost completely disappeared.

On analysis of our case, the following problems have to be considered: 1. What was the relation between the low serum potassium level and the clinical syndrome in this patient? 2. Which factors were responsible for the fall in the serum potassium level?

In order to explain the relation between the low serum potassium content and the clinical picture, we can best compare the situation with that occurring during an acute attack of familial periodic paralysis. This hereditary disease is characterized by paroxysms of muscular paralysis, during which severe dyspnea has been frequently noted. The respiratory distress during the attack is due to a paralysis of the diaphragm and the intercostal muscles. It is remarkable that the accessory respiratory muscles and the muscles which are innervated by the cranial nerves are almost never involved in the paralysis. Irregular action of the heart, cardiac dilatation and systolic murmurs during the attacks have been described.³ Biemond and Polak Daniels⁴ described "remarkable throbbing of the peripheral arteries" in their case during an attack. Changes in the electrocardiogram during the attack have been studied by Stewart and others.⁵ The serum potassium content has always been found significantly low during the attack whenever it has been determined.⁶ Administration of potassium salts causes a rapid disappearance of the paralysis together with the other signs.

3. Talbot, J. H.: Period Paralysis, *Medicine* **20**:85, 1941.

4. (a) Biemond, A., and Polak Daniels, A.: Over het verband tusschen paroxysmale verlamming en progressive spierdystrophie, *Nederl. tijdschr. v. geneesk.* **78**:1071, 1934; (b) Familial Periodic Paralysis and Its Transition into Spinal Muscular Atrophy, *Brain* **57**:91, 1934.

5. Stewart, H. J.; Smith, J. J., and Milhorat, A. T.: Electrocardiographic and Serum Potassium Changes in Familial Period Paralysis, *Am. J. M. Sc.* **199**:709, 1940.

6. (a) Aitken, R. S.; Allott, E. N.; Castleden, L. I. M., and Walker, M.: Observations on a Case of Familial Periodic Paralysis, *Clin. Sc.* **3**:47, 1937. (b) Allott, E. N., and McArdle, B.: Further Observations on Familial Periodic Paralysis, *ibid.* **3**:229, 1938. (c) Pudenz, R. H.; McIntosh, J. F., and McEachern, D.: The Role of Potassium in Familial Periodic Paralysis, *J. A. M. A.* **111**: 2253 (Dec. 17) 1938. (d) Talbot.³ (e) Biemond and Polak Daniels.^{4b}

LOW SERUM POTASSIUM LEVEL DURING RECOVERY FROM DIABETIC COMA

With Special Reference to Its Cardiovascular Manifestations

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AMSTERDAM

DURING the treatment of a patient with severe diabetic coma, we had the opportunity to observe an alarming clinical syndrome, which was probably due to a condition of extreme potassium depletion.

REPORT OF A CASE

Mrs. B., aged 56 and mother of five children, was admitted to the hospital on July 27, 1946, at 8 p. m. in severe diabetic coma. The past history was noncontributory but for the fact that she had been extremely obese as a young girl and that she was known to have had diabetes for twelve years. She took 20 units of regular insulin daily but was always negligent about her diet. No members of her family were known to have suffered from any special diseases. There was no history of periodic muscular paralysis in the family.

On July 23 the patient noticed a furuncle on her nose. She was tired and thirsty and had a complete lack of appetite. She drank a lot, and about every fifteen minutes she had to void urine. On July 26 she began to vomit. On July 27 she awoke with intense pain in the upper abdominal area. During the rest of the day she became increasingly drowsy. She had omitted her insulin since July 23.

Physical Examination.—Examination on admission of the patient to the hospital revealed an emaciated, dehydrated woman in deep coma with acidotic respiration. There was a strong acetone odor of the breath. The eyeballs were extremely soft. The pulse was regular with a frequency of 98 per minute, and the respiratory rate was 32. The rectal temperature was 36 C. (96.8 F.) and the blood pressure 160 systolic and 80 diastolic. There was a furuncle on the nose. No other significant abnormalities were found on internal examination. Neurologic examination revealed narrow, sluggish pupils and the absence of tendon reflexes.

Laboratory Examination.—Urinalysis gave strongly positive reactions for albumin, glucose, acetone and diacetic acid. The sediment contained erythrocytes and short granular casts. Chemical examination of the blood on admission gave these values: glucose, 486 mg.; plasma bicarbonate, 6 volumes per cent (2.7 milliequivalents); urea, 65 mg.; serum chloride, 376 mg. (103 milliequivalents); sodium, 340 mg. (148 milliequivalents), and potassium, 20.8 mg. (5.3 milliequivalents) per hundred cubic centimeters.

From the Second Medical Service of the Wilhelmina Gasthuis.

Different factors cooperated to cause the drop in serum potassium in our patient. For an understanding of the situation, it is best to distinguish between the potassium balance which existed at the time of admission and the influence thereon of the ensuing therapy. Before and during the first hours of hospitalization, the patient had not taken any food; she had ingested only large quantities of water. The classic researches of Atchley, Loeb, Dickinson, Benedict and Driscoll¹¹ and those of Wiley and Wiley and Waller¹² have shown that a considerable loss of potassium through the urine occurs during diabetic acidosis. This loss is probably due to a combination of the copious diuresis and the increased glycosuria (case 2 in the study by Atchley and others), acidosis (case 1 in the same study) and dehydration.^{12b}

There may be other causes for this loss of potassium. It is well known that in untreated diabetes part of the body protein from the cells liberates nitrogen as well as large quantities of potassium and phosphorus, and these substances are consequently excreted in the urine. The vomiting and gastric lavage may also have contributed to the loss of potassium. Gastric juice contains not inconsiderable amounts of potassium—according to Austin and Gammon¹³ two and one-half times as much as blood serum. We have frequently found the potassium content of vomitus to be between 40 and 50 mg. per hundred cubic centimeters.¹⁴

Thus, it may be assumed that at the moment when treatment was started our patient had ingested little potassium and had lost a considerable quantity. This potassium depletion of the body must have resulted in a diminution of the intracellular potassium stores. Probably there was also a diminution of the volume in the extracellular fluid. However, although the potassium balance was already negative when the patient came in, the potassium level of the serum had remained normal up to this point. It only began to fall when treatment was instituted. This treatment consisted in administration of large amounts of insulin, water, dextrose, sodium chloride and sodium bicarbonate

11. Atchley, D. W.; Loeb, R. F.; Dickinson, W. R.; Benedict, E. M., and Driscoll, M. E.: On Diabetic Acidosis: A Study of Electrolyte Balances Following the Withdrawal and Re-Establishment of Insulin Therapy, *J. Clin. Investigation* **12**:297, 1933.

12. (a) Wiley, F. H.; Wiley, L. L., and Waller, D. S.: The Effect of the Ingestion of Sodium, Potassium, and Ammonium Chloride and of Sodium Bicarbonate on the Metabolism of Inorganic Salts and Water, *J. Biol. Chem.* **101**:73, 1933. (b) Wiley, F. H., and Wiley, L. L.: The Inorganic Salt Balance During Dehydration and Recovery, *ibid.* **101**:83, 1933.

13. Austin, J. H., and Gammon, G. D.: Gastric Secretion After Histamine: Sodium and Potassium Content and Pepsin Estimation, *J. Clin. Investigation* **10**:287, 1931.

14. Frenkel, M.; Groen, J., and Willebrands, A. F.: Unpublished observations.

7. The neck veins were engorged to about 7 cm. above the level of the angulus Ludovici. There were no signs of pulmonary edema.

What could be the cause of this alarming syndrome in a patient who only a few hours before appeared to be recovering satisfactorily from her coma? We knew from previous experience that overdosage of insulin was sometimes accompanied with a fall in the serum potassium level. We further knew from the literature on familial periodic paralysis and other conditions accompanied with a low serum potassium level that such a fall can occur together with a typical clinical syndrome. We had been struck, in reading some descriptions of the attack of periodic paralysis, by the combination of muscular weakness with respiratory distress and irregularities of the pulse. This led us to suspect that the alarming syndrome in this patient who had been treated with unusually large quantities of insulin might be due to a low serum potassium level. Accordingly, we took blood for a potassium determination, and without waiting for the result we administered twice, at short intervals, 2 Gm. of potassium chloride in solution by mouth. The effect was striking. Within half an hour the patient gave a completely different impression. She became interested in her surroundings and asked for food. Her respiration became normal. Muscular weakness, irregularity of the pulse and cardiac murmur had disappeared. The blood pressure one-half hour after the first dose of potassium chloride was 135 systolic and 80 diastolic. The venous pressure was normal. Further recovery was uneventful. A few hours later the report came back from the laboratory that the serum potassium, which had been 20.8 mg. per hundred cubic centimeters on admission, had fallen at the critical moment to 7.4 and 6.3 mg. (duplicate estimations, averaging 1.8 milliequivalents). After the administration of potassium, the level was not determined until the next day, when it had risen to 13.5 mg. per hundred cubic centimeters. A few days later, after the patient had completely recovered, we found normal values of 24 to 25 mg.

COMMENT

About one month after this observation, we received *The Journal of the American Medical Association* of Aug. 10, 1946, in which Holler² described a case which in many respects was similar to ours. His patient was a diabetic girl of 18 years who was admitted to the hospital in coma. She also received intensive treatment with insulin and a solution of dextrose and sodium chloride. Of the latter, she got 17 liters by vein during the first twenty-four hours. After the first twelve hours of treatment, she became restless and dyspneic. The respiratory distress was due to a paralysis of the diaphragm and the lower intercostal muscles; it became so severe after twenty-four hours that she had to be placed in a Drinker respirator. Several attempts to take her out of the respirator resulted in a distressing recurrence of the dyspnea. After twenty-four hours, about twelve hours after the first appearance of the alarming signs, the possibility of a potassium depletion was considered. The serum potassium was at this time 9.8 mg. per hundred cubic centimeters. Potassium chloride was administered by vein and

2. Holler, J. W.: Potassium Deficiency Occurring During the Treatment of Diabetic Acidosis, *J. A. M. A.* **131**:1186 (Aug. 10) 1946.

coma confirm the former observations that as soon as insulin is given excretion of potassium in the urine decreases.

The migration of potassium from the extracellular fluid into the cells does not take place with low blood sugar levels only. It is a regular part of a physiologic mechanism, inherent in the action of insulin. In other patients with diabetic coma¹⁴ we have maintained high blood sugar levels throughout the treatment by administering large quantities of dextrose together with the insulin. Nevertheless, these patients showed a similar drop in serum potassium.

Most patients with diabetic coma do not show any clinical manifestations associated with this potassium shift. If the patient is given food early during the treatment, the shift is masked by the concomitant intake of potassium and there will be no drop in serum potassium. In other cases, the serum potassium may drop, but the shift of potassium from extracellular to intracellular space is not decided enough to cause clinical manifestations, and therefore it is not noted. Only in cases of severe diabetic coma, as in Holler's and in our case, in which the potassium stores of the body were already depleted on entry, no food (and hence no potassium) was given and unusually large amounts of insulin were administered, may the level of potassium drop so low. The potassium shift may then produce the clinical syndrome of generalized muscular insufficiency. It does not seem improbable, however, that this syndrome has been overlooked in a number of cases, and it may have been the cause of the "unexplained" death of patients with diabetic coma in spite of correction of the shock and the chemical abnormality of the blood.²² Of these deaths, Wilder,²³ stated: "Usually they are sudden deaths, suggesting pulmonary embolism and shock or acute dilatation of the heart, but at necropsy no emboli can be found and the heart is not greatly dilated. In some such cases the heart stops before the respiration, although in other cases respiratory failure occurs first." Joslin and others²⁴ have also commented on the unexplained death of some patients with diabetic coma in whom a "gasping respiration" develops. The modern tendency to bring the patient with diabetic acidosis out of his coma within the shortest possible time may actually contribute to the occurrence of this dangerous situation.

It is more difficult to evaluate the effect of the other therapeutic measures on the development of the "potassium depletion syndrome." Our patient, as well as Holler's, received large quantities of fluid to com-

22. Butler, A. M., in discussion on Diabetes Mellitus with Acidosis, Cabot Case 30451, *New England J. Med.* **231**:657, 1944.

23. Wilder, R. M.: *Clinical Diabetes Mellitus and Hyperinsulinism*, Philadelphia, W. B. Saunders Company, 1941, P. 180.

24. Joslin, E. P.; Root, H. F.; White, P., and Marble, A.: *Treatment of Diabetes Mellitus*, ed. 8, Philadelphia, Lea & Febiger, 1946.

In other conditions of potassium depletion, muscular paralysis together with shortness of breath, cardiac arrhythmia and changes in the electrocardiogram have also been described. Brown, Currens and Marchand⁷ observed similar symptoms in 2 cases of chronic nephritis with low serum potassium. Administration of potassium resulted in rapid relief of the symptoms. Thorn and his co-workers⁸ witnessed two attacks of transient paralysis associated with an abnormal lowering of the serum potassium level in a patient with Addison's disease who had been given large quantities of desoxycorticosterone in addition to intravenously administered sodium chloride and dextrose. In consideration of these facts, it seems justified to suppose that various conditions in which a considerable drop in serum potassium takes place may also give rise to a disturbance of muscle metabolism of such a degree that it may result in paralysis of the extremities, in respiratory paralysis and in a disturbance in the function of the heart muscle. The experiments of Kuhlmann⁹ and of Ferrebee and others¹⁰ support this hypothesis. After administration of large doses of desoxycorticosterone in dogs, these authors observed a drop in serum potassium which was sometimes accompanied with muscular paralysis.

It is not known at present if there exists a critical level below which the serum potassium must fall before the syndrome of generalized muscular paralysis makes its appearance. Aitken, Allott, Castleden and Walker^{6a} reported that an attack occurred in their patient with familial periodic paralysis as soon as the serum potassium dropped below 12 Gm. per hundred cubic centimeters. Allott and McArdle,^{6b} however, found a less rigid relationship between the serum potassium level and the occurrence of the attacks. In view of further experiences with other patients, we are inclined to doubt that there is such a thing as a critical serum potassium level, but it is certain that the content must be significantly lowered before clinical manifestations can be expected.

7. Brown, M. R.; Currens, J. H., and Marchand, J. F.: Muscular Paralysis and Electrocardiographic Abnormalities Resulting from Potassium Loss in Chronic Nephritis, *J. A. M. A.* **124**:545 (Feb. 26) 1944.

8. Thorn, G. W.: Desoxycorticosterone, *J. Mt. Sinai Hosp.* **8**:1177, 1942. Thorn, G. W.; Dorrance, S. S. and Day, E.: Addison's Disease: Evaluation of Synthetic Desoxycorticosterone Acetate Therapy in One Hundred and Fifty-Eight Patients, *Ann. Int. Med.* **16**:1053, 1942.

9. Kuhlmann, D.; Ragan, C.; Ferrebee, J. W.; Atchley, D. W., and Loeb, R. F.: Toxic Effects of Desoxycorticosterone in Dogs, *Science* **90**:496, 1939.

10. Ferrebee, J. W.; Parker, D.; Carnes, W. H.; Gerity, M. K.; Atchley, D. W., and Loeb, R. F.: Replacement of Potassium by Sodium in Muscles of Normal Dogs Receiving Desoxycorticosteroneacetate, *J. Clin. Investigation* **20**:445, 1941; Certain Effects of Desoxycorticosterone: Development of Diabetes Insipidus and Replacement of Muscular Potassium by Sodium in Normal Dogs, *Am. J. Physiol.* **135**:230, 1941.

described by Kugelmann²⁶ and by Lauter and Baumann²⁷ in hypoglycemic shock. We consider it more likely that these phenomena are due to the concomitant potassium changes rather than to a low blood sugar level. The fact that we observed them in a patient who was not hypoglycemic and that they did not disappear after administration of dextrose but did so after administration of potassium supports this assumption. In the third place, the regular association of certain changes in the electrocardiogram with this condition of potassium shift seems of interest. Here again, it is striking that the electrocardiographic changes which have been described after overdosage of insulin are exactly the same as those seen with a low serum potassium level²⁸ and during the attacks of periodic paralysis.⁵ They consist essentially in a depression of the S-T segment and in low voltage of the T waves. We suppose that the electrocardiographic changes observed by Bellet and Dyer²⁹ in patients who recovered from diabetic coma are probably due to the same mechanism. We suggest that these changes are due not to a low blood sugar level, as has sometimes been assumed, but to a shift of potassium from extracellular to intracellular space inside the heart muscle. Actually, several investigators have observed that the changes in the electrocardiogram after overdosage of insulin may occur with an insignificant drop of the blood sugar level whereas they are sometimes absent when the blood sugar level is extremely low.^{27a}

It is too early to decide whether this shift in potassium and the clinical effects thereof are a direct result of the action of insulin. The possibility should also be borne in mind that they are due to an increased secretion of epinephrine or of one of the adrenal cortex hormones taking place as a counter regulation after overdosage of insulin. We also feel that it is unjustified to ascribe the clinical syndrome associated with the potassium shift to the low serum potassium level itself. It seems more probable that changes in the intracellular potassium occurring with this shift are responsible.

SUMMARY

During treatment of a patient in severe diabetic coma with large quantities of insulin, water, dextrose, sodium chloride and sodium bicarbonate, we observed a syndrome of muscular weakness, gasping type of respiration due to paralysis of the lower respiratory tract,

26. Kugelmann, B.: Ueber die Beziehungen zwischen Insulin und Adrenalin im menschlichen Organismus, *Klin. Wchnschr.* **10**:59, 1938.

27. Lauter, S.; and Baumann, H.: Kreislauf und Atmung im hypoglycaemischen Zustand, *Deutsches Arch. f. klin. Med.* **163**:161, 1929.

28. (a) Scherf, D., and Boyd, L. D.: *Clinical Electrocardiography*, London, William Heinemann, Ltd., 1945. (b) Brown and others.⁷ (c) Holler.²

29. Bellet, S., and Dyer, W. W.: The Electrocardiogram During and After Emergence from Diabetic Coma, *Am. Heart J.* **13**:72, 1937.

(still no potassium). How is the drop in the serum potassium which occurred with these measures to be explained?

As early as 1923 and 1924 Harrop and Benedict¹⁵ and Briggs, Koechig, Doisy and Weber¹⁶ described a drop in serum potassium after injection of large doses of insulin in persons with diabetes, in normal persons and in experimental animals. Their observations were confirmed by different authors, especially by Kerr¹⁷ in pancreatectomized dogs. Later a low serum potassium level was found by Harris, Blalock and Horwitz¹⁸ in patients with psychosis during induced insulin shock. In Holland, a low serum potassium content during induced hypoglycemic shock was described by Drooglever Fortuyn.¹⁹ Recently, we determined the serum potassium in 2 diabetic patients who were admitted in hypoglycemic coma.¹⁴ The levels were 13 and 14 mg. per hundred cubic centimeters respectively.

Most investigators ascribe the drop in serum potassium to the fact that insulin causes the potassium to shift from the extracellular fluid into the cells.²⁰ Some believe that potassium as well as phosphate is used up in one of the first stages of storage or combustion of carbohydrate by the action of insulin. Another possibility is that potassium, together with water, is taken up by the hepatic cells during the synthesis of glycogen (Fenn²¹). A third hypothesis, which seems likely, is that during the rapid correction of the metabolic disturbance which takes place during treatment of diabetes proteins, which had been destroyed during the coma, are being rebuilt. This synthesis requires the fixation of water and potassium in the cells. Which of these hypothetical mechanisms actually plays the most important role is undecided. The only thing that is known for certain is that the potassium which disappears from the extracellular fluid after the administration of insulin is not excreted in the urine. Our own experiences with other cases of diabetic

15. Harrop, G. A., and Benedict, E. M.: The Participation of Inorganic Substances in Carbohydrate Metabolism, *J. Biol. Chem.* **59**:683, 1924.

16. Briggs, A. P.; Koechig, I.; Doisy, E. A., and Weber, C. J.: Some Changes in the Composition of the Blood Due to the Injection of Insulin, *J. Biol. Chem.* **58**:721, 1923.

17. Kerr, S. E.: The Effect of Insulin and Pancreatectomy on the Distribution of Phosphorus and Potassium of the Blood, *J. Biol. Chem.* **128**:35, 1938.

18. Harris, M. M.; Blalock, J. R., and Horwitz, W. A.: Metabolic Studies During Insulin Hypoglycemia Therapy of Psychosis, *Arch. Neurol. & Psychiat.* **40**:116, (July) 1938.

19. Drooglever Fortuyn, J.: Hypoglycemia and the Autonomic Nervous System, *J. Nerv. & Ment. Dis.* **93**:1, 1941.

20. Guest, G. M.: Organic Phosphates and Mineral Metabolism in Diabetic Acidosis, *Am. J. Dis. Child.* **64**:401 (Sept.) 1942.

21. Fenn, W. O.: The Deposition of Potassium and Phosphate with Glycogen in Rat Livers, *J. Biol. Chem.* **128**:297, 1939; The Role of Potassium in Physiological Processes, *Physiol. Rev.* **20**:337, 1940.

METABOLIC STUDIES IN DIABETIC ACIDOSIS

I. The Effect of the Early Administration of Dextrose

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IT IS generally agreed that diabetic acidosis develops from excessive production of ketone in the body consequent on diminished glucose oxidation and depletion of liver glycogen. In order to check production of ketone, therapeutic efforts have been directed toward acceleration of glucose oxidation and restoration of liver glycogen. Soskin¹ and Mirsky² have found that the maintenance of considerable hyperglycemia through the intravenous injection of large amounts of dextrose accelerated glucose oxidation and glycogenesis in the liver and the disappearance of ketosis. For this reason it had been our custom to begin administration of dextrose early in the treatment of diabetic coma, while hyperglycemia was still present. However, the development of fatal circulatory collapse or cardiac failure during the course of therapy has led us to reevaluate the effects of early administration of large amounts of dextrose on the carbohydrate metabolism, acidosis, water balance and clinical course of diabetic coma.

PROCEDURE

The studies reported in this paper were carried out during the first twenty-four hours of hospitalization on 28 patients admitted in severe

Supported in part by gifts obtained through the efforts of the late Dr. Alpheus Jennings and his staff.

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1. Soskin, S., and Levine, R.: A Relationship Between the Blood Sugar Level and the Rate of Sugar Utilization Affecting the Theory of Diabetes, *Am. J. Physiol.* **120**:761, 1937.

2. Mirsky, I. A.; Heiman, J. D., and Broh-Kahn, R. H.: The Antiketogenic Action of Glucose in the Absence of Insulin, *Am. J. Physiol.* **118**:290, 1937.

bat dehydration. In our case 5,000 cc. was administered during the first twelve hours; Holler's patient received 17,000 cc. in twenty-four hours, of which 15,000 cc. was eliminated by the kidneys during the same time. Part of this fluid was retained in the rehydrated body cells together with potassium. Another part of the retained water diluted the extracellular fluid. It seems probable that this rehydration with a fluid not containing any potassium contributed to the fall in serum potassium concentration.

The administration of large amounts of dextrose may cause a fall in the serum potassium level in normal subjects. Aitken and others^{6a} found a serum potassium level of 16 mg. per hundred cubic centimeters in normal subjects after ingestion of 250 Gm. of dextrose. The underlying mechanism is probably the same as that occurring after administration of insulin. An extremely low serum potassium level, as was found in our case, has never been obtained, however, by administration of dextrose alone. We do not believe that 18 Gm. of sodium chloride, which our patient received in isotonic solution, can have played a major role. The influence of the administration of large quantities of sodium bicarbonate (50 Gm. in our case) on potassium metabolism is not completely elucidated. Darrow²⁵ observed a loss of muscular potassium and sometimes a decrease in serum potassium after intraperitoneal injection of sodium bicarbonate in rats. We¹⁴ observed a drop of the serum potassium level in 2 patients after administration of 1,000 cc. of a 5 per cent solution of sodium bicarbonate by vein. The mechanism of this drop, however, is entirely different from what we observed in the case under discussion, because it was found that the infusion of sodium bicarbonate gave rise to an increased excretion of potassium in the urine.

Finally, we wish to stress that in the syndrome of potassium depletion combined with a potassium shift into the cells, as we have seen it in our patient, three different groups of phenomena should be distinguished. The first group consists in muscular paralysis and dyspnea. This may be called the syndrome of generalized muscular insufficiency. In the second place, our patient showed a number of circulatory phenomena: (1) an increased pulse pressure; (2) a collapsing pulse; (3) an increase of the cardiac dullness; (4) a systolic murmur, and (5) a high venous pressure. This is the cardiovascular syndrome known as "high output failure" or "arteriovenous shunt syndrome." We feel that it forms part of the clinical syndrome associated with this particular disturbance of potassium metabolism. We had the opportunity since to observe the same syndrome several times in instances of insulin overdosage. The large pulse pressure as well as the high venous pressure has been

25. Darrow, D.: Changes in Muscle Composition in Alkalosis, *J. Clin Investigation* 25:324, 1946.

toluene in fractional specimens in the intervals between the collection of blood samples. Quantitative urinalyses were made for (1) phosphorus by the method of Fiske and Subbarow,⁸ (2) glucose by the method of Benedict,⁸ (3) chloride by the Volhard-Arnold method⁹ and (4) nitrogen by the method of Koch and McMeekin.¹⁰ Qualitative urinalyses were also made hourly for acetone and glucose. Fecal analyses were not made because of the short duration of the experiment. Gastric lavage was performed routinely within the first hour.

For purposes of presentation, the data were condensed to cover four periods. The number of hours elapsing between the onset of therapy and the end of each period is given for every case in table 1. The first period began with the onset of therapy and extended for an average of four to five hours. The second period corresponded roughly with the second four to five hours of therapy except in the phosphate group, for which the second period included only the interval from the beginning to the end of sodium phosphate administration. The third period extended from the eighth or ninth hour to the fourteenth to sixteenth hour of therapy. The fourth period covered the remaining time up to the termination of the study between the twenty-third and twenty-fourth hour. Clinical observations and results of blood analyses recorded in the tables represent values obtained at the end of the corresponding period. All values for intake, urinary output and balance for each period are recorded in terms of grams, milligrams or cubic centimeters per hour for purposes of comparing data in periods of unequal length.

Although the discussion of the effects of sodium phosphate will be reserved for another paper, it was convenient to present the data on the patients receiving it in the same tables with the data on the saline and dextrose groups. Since the treatment of the phosphate group in the first period was similar to that of the dextrose group, these two groups will be taken as a unit for the duration of the first period. Thereafter, only the dextrose group will be contrasted with the saline group.

For fatality rates and for data on the rate of disappearance of acetonuria the study was extended to include a total of 71 cases.

STATUS OF THE PATIENTS ON THEIR ADMISSION TO THE HOSPITAL

All patients had severe diabetic acidosis. The significant clinical and laboratory findings on their admission to the hospital are summarized in tables 1, 2 and 3. Carbon dioxide-combining power averaged 13.4

8. Benedict, S. R.: The Detection and Estimation of Glucose in the Urine, *J. A. M. A.* **57**:1192 (Oct. 7) 1911.

9. Hawk, P. B., and Bergeim, O.: *Practical Physiological Chemistry*, ed. 11, Philadelphia, P. Blakiston's Son & Co., 1937, p. 768.

10. Koch, F. C., and McMeekin, T. L.: A New Direct Nesslerization Microkjeldahl Method and a Modification of the Nessler-Folin Reagent for Ammonia, *J. Am. Chem. Soc.* **46**:2066, 1924.

irregular Corrigan's pulse, large pulse pressure, dilatation of the heart, a systolic murmur and high venous pressure. Abnormalities of the electrocardiogram have also been noted in this condition. The syndrome manifested itself after the blood sugar and blood bicarbonate levels had returned to normal. It was found that the serum potassium content, which had been normal on the patient's admission to the hospital, had fallen to 6.9 mg. per hundred cubic centimeters. The conclusion is reached that this drop was most likely caused by a loss of potassium from the body during the period of acidosis, a low potassium intake for several days and a shift of potassium from extracellular to intracellular fluid under the influence of large doses of insulin.

It has been the purpose of this paper to (1) describe how, during a too energetic treatment of diabetic coma, a dangerous condition may occur which is due to potassium depletion, (2) draw attention to a typical clinical syndrome which may be a manifestation of this condition, (3) stress the value of early recognition of this complication, as it can be treated successfully by the administration of potassium, and (4) suggest the possibility that some of the vegetative manifestations of insulin "shock" are due not to hypoglycemia but to a shift of potassium from extracellular to intracellular space.

NOTE: Since this paper was submitted for publication, the following pertinent articles have appeared in the literature: Martin, H. E., and Wertman, M.: Serum Potassium, Magnesium and Calcium Levels in Diabetic Acidosis, *J. Clin. Investigation* **26**:271, 1947. Nicholson, W. M., and Branning, W. S.: Potassium Deficiency in Diabetic Acidosis, *J. A. M. A.* **134**:1292 (Aug. 16) 1947.

TABLE 2.—*Status Before Treatment, Divided According to Therapeutic Regimen*

Group	No. of Cases	Age, Yr.	Mental State	Compl- cations on Admis- sion	Blood Pressure	Severity Index, %	Blood Sugar, Mg. %	Carbon Dioxide- Combining Power, Vol. %	Plasma Chloride, Mg. %	Hemato- crit Reading	Specific Gravity	Plasma Phos- phorus, Mg. %
Saline.....	7	34	2.0	1.1	121/83	24	501	10.1	485	54.7	1.033	8.9
Dextrose.....	11	37.9	2.5	1.8	112/72	37	457	14.0	496	54.7	1.029	7.9
Phosphate.....	10	36.7	3.1	1.6	107/64	42	495	11.7	501	54.1	1.031	7.2
Average.....	28	37.8	2.6	1.6	113/70	35	482	13.4	494	54.3	1.031	7.87

TABLE 3.—*Status Before Treatment, Divided According to Survival*

Group	No. of Cases	Age, Yr.	Mental State (0 to 4)	Compl- cations on Admis- sion	Blood Pressure	Severity Index, %	Blood Sugar, Mg. %	Carbon Dioxide- Combining Power, Vol. %	Plasma Chloride, Mg. %	Hemato- crit Reading	Specific Gravity	Plasma Phos- phorus, Mg. %
Survivors.....	20	34.1	2.1	3.3	122/75	25	474	13.8	499†	54.8	1.031	7.1
Dead.....	8	49.6	3.8	0.9	91/60	62	504	12.4	483*	53.6	1.031	8.7
Average.....	28	37.8	2.6	1.6	113/70	35	482	13.4	494†	54.3	1.031	7.9

* Seven cases.

† Seventeen cases.

‡ Twenty-four cases.

diabetic acidosis or coma. Complete physical examination was made on admission, and special attention was directed to the cardiovascular status and to the presence of other complications. Frequent observations were made of the mental state, blood pressure and degree of hydration throughout the course of therapy. For the sake of uniformity, the clinical observations were made throughout by us.

Accurate records were kept of all intake. This was limited to water, sodium chloride, dextrose and insulin, supplemented in some cases by crystalline vitamins, alkali, plasma, blood or sodium phosphate. The cases were divided into three groups, according to therapeutic regimen. The first group received no supplementary dextrose until the blood sugar level had fallen within the normal range. (This group is hereafter referred to as the "saline" group.) The second group received dextrose intravenously or orally from the onset of therapy (hereafter called the "dextrose" group). The third group were also started on dextrose early, but in addition they received buffered sodium phosphate solution beginning within three and one-half to nine hours after the onset of therapy (hereafter designated as the "phosphate" group). The discussion of the course of the phosphate group after the first four hours is reserved for another paper.

Samples of heparinized blood were collected immediately after admission of the patients to the hospital and at approximately four hour intervals thereafter. Each specimen was analyzed for (1) inorganic phosphorus by the method of Fiske and Subbarow,³ (2) glucose by the method of Folin and Wu,⁴ (3) chloride by the method of Saifer and Kornblum⁵ and (4) carbon dioxide-combining power by the method of Van Slyke and Cullen.⁶ Hematocrit readings were done with accurately graduated centrifuge tubes and the specific gravity of the plasma was determined by the falling drop method of Phillips, Van Slyke and others,⁷ with copper sulfate standards.

An indwelling catheter was installed, and the bladder was emptied prior to the onset of therapy. All urine thereafter was collected under

3. Fiske, C. H., and Subbarow, Y.: The Colorimetric Determination of Phosphorus, *J. Biol. Chem.* **66**:375, 1925.

4. Folin, O., and Wu, H.: A Simplified and Improved Method for the Determination of Sugar, *J. Biol. Chem.* **41**:367, 1920.

5. Saifer, A., and Kornblum, M.: Determination of Chlorides in Biological Fluids by the Use of Adsorption Indications, *J. Biol. Chem.* **112**:117, 1935.

6. Van Slyke, D. D., and Cullen, G. E.: Studies of Acidosis: I. The Bicarbonate Concentration of the Blood Plasma; Its Significance and Its Determination as a Measure of Acidosis, *J. Biol. Chem.* **30**:289, 1917.

7. Phillips, R. A.; Van Slyke, D. D.; Dole, V. P.; Emerson, K., Jr.; Hamilton, P. B., and Archibald, R. M.: The Copper Sulfate Method for Measuring Specific Gravities of Whole Blood and Plasma, *Bull. U. S. Army M. Dept.*, 1943, no. 71, p. 66.

Since the prognosis in diabetic coma depends on many factors, a method of grading the status on the patient's admission to the hospital was deemed essential to the evaluation of results from different therapeutic regimens. The method of Collen¹³ was selected as the best guide to prognosis. Collen analyzed the relation of all the previously mentioned factors to the ultimate outcome and concluded that prognosis was influenced chiefly by the age, mental state, diastolic blood pressure and the presence of complications serious enough in themselves to threaten life. He derived the following formula as the most accurate representation of the fatality rate in his series:

Severity index =

$$\frac{30 (\text{mental state} + \text{complications}) + 50 + \text{age} - \text{diastolic B.P.}}{4}$$

The mental state was graded 0 to 4 as has been described. Complications were graded by Collen 0 to 5 in terms of their danger to the life of the patient.¹⁴

The severity index was determined for each patient in this series and varied from 3 to 82 per cent, averaging 35 per cent. Of the 10 patients in this series whose severity index was above 40 per cent, 8 died; of the 18 with severity indexes below 40 per cent, all recovered. The importance of the factors stressed by Collen in determination of the final outcome was borne out in this small series, as shown in table 3. Only 3 of the 9 patients over 40 years of age survived, whereas 17 of the 19 below 40 recovered. Four of the 6 patients whose blood pressures were at shock levels on admission to the hospital died.¹⁵ Eight of the 15 unconscious patients died. All fatalities occurred in patients who were unconscious on admission. Despite the dire prognostic significance of the presence of unconsciousness, irreversible damage to the central nervous system did not seem to be the major cause of death, since 4 of the 8 patients who failed to react to painful stimuli on admission to the hospital regained consciousness and the other 4 responded to stimuli before they relapsed and died.

Although choice of therapeutic regimen was made at random, subsequent analyses revealed a distinct difference in the severity of the condition in the three groups. This was reflected in average severity indexes of 24 per cent for the saline group, 37 per cent for the dextrose group and 42 per cent for the phosphate group. The main differences between the groups lay in the depression of consciousness, the drop in diastolic blood pressure and the severity of complications, all of which

13. Collen, M. F.: Mortality in Diabetic Coma, *Arch. Int. Med.* **70**:347 (Sept.) 1942.

14. As stated previously, the complications in our series were graded 0 to 4 rather than 0 to 5 as in Collen's work.

15. The blood pressures in the remaining 4 fatal cases were probably at shock levels for the originally hypertensive patients involved.

TABLE 1.—*Clinical Status*

Group	Case	Experimental Periods Hours Elapsed from Admission to End of Period				Age, Yr.	Com- plica- tions * on Admis- sion	Mental State * at End of Period				Admis- sion	Blood Pressure at End of Period				Severity Index, %	Deaths
		1	2	3	4			1	2	3	4		1	2	3	4		
Saline.....	1	4.00	8.00	16.00	24.00	43	1	1	1	1	1	1	130/90	140/90	140/90	140/90	15	—
	2	5.50	10.50	17.50	24.00	30	1	1	1	1	2	120/84	—	—	110/80	14	—	
	3	4.00	10.00	16.00	24.00	26	0	2	0	0	0	86/74	90/70	90/70	90/70	15	—	
	4	6.00	10.00	16.00	24.00	28	1	2	2	1	0	110/40	112/54	110/70	110/70	30	—	
	5	4.50	6.50	12.50	24.00	39	0	1	1	1	0	100/80	104/70	98/60	90/70	10	—	
	6	5.50	—	—	—	55	4	4	—	—	—	130/80	136/76	—	—	64	D	
	7	6.00	13.00	18.50	24.00	17	1	2	1	1	0	123/80	100/75	—	—	19	—	
Average.....		5.07	9.67	16.08	24.00	34	1.1	2.0	1.7	1.0	0.7	121/83	110/75	111/69	112/77	24	14%	
Dextrose.....	8	5.00	8.00	11.50	18.50	67	4	4	4	4	3	4	70/40	70/50	60/40	56/40	82	D
	9	5.75	10.50	16.00	24.00	26	1	1	0	0	0	0	118/70	116/70	60/30	110/72	17	—
	10	4.00	7.50	12.50	—	51	4	3	1	3	—	85/65	110/60	106/58	58/28	61	D	
	11	4.00	10.00	18.00	24.00	32	1	1	1	1	1	1	140/100	136/82	112/92	112/92	11	—
	12	4.00	8.00	16.00	24.00	65	0	2	2	1	0	0	108/50	152/60	—	140/70	31	—
	13	5.25	8.25	17.00	—	30	2	4	4	4	4	—	60/40	84/44	90/30	84/24	55	D
	14	6.00	10.00	17.00	23.50	40	3	4	4	4	4	4	116/74	130/0	118/85	125/80	57	D
	15	4.00	8.00	16.00	24.00	37	2	2	2	1	0	0	110/60	130/75	108/72	120/80	37	—
	16	3.00	6.33	17.00	24.00	20	0	2	2	2	1	0	120/80	120/78	120/10	118/80	13	—
	17	4.00	8.00	17.00	—	31	0	3	2	1	1	1	130/90	123/68	135/80	125/80	20	—
	18	4.00	8.00	16.00	24.00	18	3	1	1	1	1	0	120/80	—	—	—	27	—
Average.....		4.45	9.30	15.82	23.25	37.9	1.8	2.5	2.3	1.8	1.6	112/72	117/58	103/74	104/57	37	36%	
Phosphorus...	19	3.17	4.17	16.00	24.00	23	0	4	4	1	1	0	130/80	105/65	98/53	110/70	30	—
	20	3.50	4.50	—	—	31	3	3	2	1	—	—	108/60	130/58	—	—	43	D
	21	6.25	7.75	16.00	20.50	14	1	3	2	0	0	0	84/64	90/20	104/64	102/60	43	—
	22	3.33	4.50	12.25	24.00	69	0	1	1	1	0	0	104/70	80/60	130/60	110/70	20	—
	23	3.50	4.75	11.00	24.00	39	0	3	2	1	1	0	104/78	95/75	104/64	95/60	25	—
	24	5.75	10.25	13.50	20.50	41	3	4	2	1	4	1	120/58	170/80	180/78	—	55	D
	25	8.50	13.50	17.50	24.00	35	3	4	2	0	0	0	118/70	120/80	150/80	130/70	56	—
	26	4.25	6.75	15.33	—	62	3	4	2	2	3	—	117/52	80/40	—	—	71	D
	27	4.00	8.25	12.00	24.00	26	2	3	3	1	1	0	133/84	100/60	104/68	102/72	28	—
	28	5.67	7.75	11.50	24.00	22	1	3	3	2	2	1	90/0	98/58	108/64	110/70	48	—
Average.....		4.79	7.23	13.90	23.13	36.7	1.6	3.1	2.1	1.0	1.0	107/64	107/63	123/68	105/62	42	30%	

* Graded 0 to 4 as explained in the text.

TABLE 4.—Data Relating to the Saline, Dextrose and Phosphate Groups

Group	Case	Blood Sugar at End of Period, Mg./100 Cc.				Insulin, Units per Hour During Period				Total 24 Hour Insulin Units	Carbon Dioxide-Combining Power at End of Period, Vol. %				Hours Until Urine Was Acetone Free			
		Admis- sion	1	2	3	4	1	2	3		4	Admis- sion	1	2		3	4	
Saline.....	1	364	178	40	154	—	165	13	2	5	765	13	19	26	37	—	10	
	2	616	142	254	232	—	36	0	15	6	333	19	63†	69†	69†	77†	14	
	3	454	140	130	333	—	70	0	0	4	315	21	37	315	50	4	12	
	4	500	133	60	135	190	113	23	0	0	790	19	17	28	35	35	16	
	5	460	120	103	103	168	96	20	4	3	525	16	39	36	36	41	11	
	6	610	210	—	—	—	109	—	—	—	(900)*	14	15	—	—	—	—	
	7	476	102	80	—	—	53	30	11	0	588	11	28	33	—	—	12	
Average.....		501	146	111	163	170	91.7	14.0	5.0	3.0	554	16.1	31.1	38.4	45.4	51.0	12.5	
Dextrose.....	8	488	420	514	464	328	90	67	114	21	1,200	11	33	33	45	50	16	
	9	408	572	338	214	120	47	70	55	45	1,200	35	30	30	33	40	16	
	10	500	572	444	572	—	175	80	44	—	(1,200)*	13	12	19	26	—	14	
	11	220	300	166	105	110	37	30	11	4	435	16	21	26	35	47	5	
	12	546	376	500	570	310	66	43	46	58	1,265	14	14	17	19	30	23	
	13	444	450	408	500	—	149	47	20	—	(1,035)*	6	14	12	33	—	10.5	
	14	488	420	364	514	332	97	58	51	62	1,570	15	30	25	25	39	8	
	15	404	522	444	163	—	63	29	14	6	520	11	16	30	49	—	14	
	16	552	430	210	103	200	67	27	41	0	730	9	28	46	52	56	12	
	17	476	470	400	200	—	109	46	22	—	(920)*	10	16	17	21	—	10	
	18	500	—	410	266	266	63	58	36	4	895	14	—	46	50	50	6	
	Average.....		457	443	367	334	273	87.5	50.4	41.0	25.0	984	14.0	21.4	27.4	35.3	44.6	12.2
	Phosphorus.....	19	420	412	—	296	67	123	130	71	16	1,435	12	29	—	42	48	11
		20	572	408	534	—	—	171	50	—	—	(950)*	14	10	18	—	—	—
		21	426	454	332	236	97	110	73	39	0	1,040	8	21	27	38	41	10.5
		22	312	354	308	222	151	60	129	26	22	810	19	19	24	26	36	11
		23	444	—	500	464	174	129	40	67	32	1,340	10	—	12	16	44	11
		24	444	490	320	364	—	117	72	42	34	1,370	13	25	46	43	—	14
25		810	464	118	92	250	78	58	0	0	950	11	26	37	43	48	13	
26		454	500	500	374	66	141	80	48	—	(1,220)*	13	22	38	42	—	14	
27		616	266	284	308	66	148	59	13	10	1,005	9	24	29	35	48	12	
28		448	380	262	206	99	92	48	15	26	993	8	13	23	43	51	18	
Average.....		495	414	351	285	129	116.9	73.9	35.6	17.5	1,125	11.7	21.0	28.2	36.5	45.1	13.3	

* Not included in averages: The patients in cases 6, 10, 13, 20 and 26 died prior to period 4, and in case 17 no data were available for this period.

† This patient received 1,000 cc. of a 2 per cent solution of sodium bicarbonate in the first period.

volumes per cent on admission and exceeded 19 volumes per cent in only 2 cases.¹¹ The blood sugar ranged from 220 to 810 mg. per hundred cubic centimeters, averaging 480 mg. The reaction for glycosuria and acetonuria was graded 4 plus in all cases. The ages of the patients ranged from 14 to 69 years, averaging 37.8. The blood pressure was at shock levels in 7 cases and was below its customary level in 19 of the remaining 21.¹²

The complications have been graded 0 to 4 in terms of their danger to the life of the patient. Thus, a grade of 4 was assigned to case 6 because of a combination of a huge infected postmammectomy incision and hypertensive heart disease with auricular fibrillation, to case 8 because of hypertension complicated by hemiplegia, renal insufficiency and recent myocardial infarction and to case 10 because of arteriosclerotic heart disease, auricular tachycardia and left and right ventricular failure. These complications were classified as grade 3: lobar pneumonia and urethral stricture, case 14; postappendical pelvic abscess, case 18; eighth month pregnancy with probable toxemia, case 20; the tabetic form of dementia paralytica and hypertensive heart disease with left ventricular hypertrophy, case 24; bronchopneumonia and infected scalp wound, case 25, and advanced arteriosclerotic heart disease in case 26. A grade of 2 was assigned to case 13 because of staphylococcic otitis externa with cellulitis, to case 15 because of rheumatic mitral stenosis and insufficiency without failure and to case 27 because of streptococcic peritonsillar abscess. Such complications as infections of the upper respiratory tract, epididymitis with orchitis, mild infection of the urinary tract and mild essential vascular hypertension were classed as grade 1.

The state of consciousness was graded numerically as follows: conscious, grade 0; drowsy, grade 1; semiconscious, grade 2; unconscious, grade 3, and unconscious and unresponsive to painful stimuli, grade 4. Over one half (15) of the patients were unconscious (grade 3 or 4), 6 were semiconscious and 7 were merely drowsy.

All presented the clinical picture of dehydration. Twenty of the 28 had hemotocrit readings of 50 per cent or above, and 6 of the 8 with lower hematocrit readings were anemic. Nineteen had a plasma specific gravity of 1.030 or greater, while only 4 had a specific gravity below 1.028.

Thirteen had a blood chloride content (expressed as NaCl) below 500 mg. per hundred cubic centimeters, the lowest being 385 mg., and only 1 had a value over 545 mg.

11. Cases 3 and 9, in which the carbon dioxide-combining powers were 21 and 35 volumes per cent respectively, were included because of certain peculiarities in the course worth reporting.

12. In cases 1, 6, 11 and 20, in which the blood pressures on admission were near the upper limits of normal, there was definite evidence of antecedent hypertension.

7 of the 11 cases in the dextrose group and for most of the first twenty-four hours in 3 others in spite of relatively large doses of insulin averaging 42.3 units per hour. Of the 5 patients in whom the blood sugar was consistently above 300 mg. per hundred cubic centimeters, 4 died. Maintenance of pronounced hyperglycemia appeared to be partially responsible for the unfavorable clinical course.

2. Glycosuria (tables 5 and 6): From table 5 it is evident that the degree of glycosuria during each period was much greater in the dextrose

TABLE 6.—*Glucose Metabolism*

Group	Case	Intake, Total Gm. Period		Output, Total Gm. Period		Balance, Total Gm. Period	
		1	2+3+4	1	2+3+4	1	2+3+4
Saline.....	1	0	100.0	8.4	30.7	— 8.4	+ 69.3
	2	0	480.0	31.9	64.4	— 31.9	+415.6
	3	0	310.0	20.7	—	— 20.7	—
	4	0	505.0	40.0	20.2	— 40.0	+484.3
	5	0	360.0	10.5	—	— 10.5	—
	6	0	—	7.9	—	— 7.9	—
	7	0	510.0	4.5	—	— 4.5	—
Average.....		0	377.5	17.7	38.4	— 17.7	+322.7
Dextrose.....	8	50.0	50.0	0.0	11.4	+ 50.0	+ 38.6
	9	340.0	805.0	154.7	309.0	+183.3	+496.0
	10	25.0	—	25.3	—	— 0.3	—
	11	50.0	480.0	14.0	—	+ 36.0	—
	12	227.5	872.5	11.3	570.2	+216.2	+302.3
	13	105.0	—	22.8	—	+ 82.2	—
	14	200.0	300.0	4.6	6.5	+195.4	+293.5
	15	115.0	645.0	27.1	23.9	+ 87.9	+621.1
	16	49.0	729.0	25.4	32.5	+ 23.6	+690.5
	17	270.0	—	34.8	—	+235.2	—
	18	200.0	710.0	68.5	251.7	+131.5	+458.3
Average.....		148.3	549.2	35.3	159.3	+113.0	+415.2
Phosphorus.....	19	130.0	830.0	38.9	107.8	+ 91.1	+722.2
	20	100.0	—	35.0	—	+ 65.0	—
	21	100.0	240.0	75.8	28.4	+ 24.2	+211.6
	22	100.0	740.0	16.8	77.8	+ 83.2	+662.2
	23	100.0	283.0	77.6	—	+ 22.4	—
	24	100.0	400.0	22.2	44.8	+ 77.8	+355.2
	25	100.0	480.0	67.7	10.9	+ 42.0	+469.1
	26	150.0	—	58.0	—	+ 92.0	—
	27	50.0	650.0	19.5	80.4	+ 30.5	+569.6
	28	60.0	225.0	37.8	146.0	+ 22.2	79.0
Average.....		99.0	481.0	43.9	70.9	+ 55.1	+438.4

group than in the saline group. A comparison of the two groups during the third period reveals that the greater glycosuria in the dextrose group cannot be attributed exclusively to the higher intake. During this period this group received an average of 27.4 Gm. per hour and excreted 7.0 Gm. per hour, or 26 per cent, whereas the saline group received 26.9 Gm. per hour and excreted only 2.0 Gm. per hour, or 7 per cent of the intake. The difference in the degree of glycosuria was due chiefly to the fact that the blood sugar level from the beginning to the end of this period was markedly elevated in the dextrose group (ranging from 367 to 334 mg.

were least in the saline group (table 1). The three groups differed only slightly with respect to age, initial blood sugar content, carbon dioxide-combining power, chloride and plasma inorganic phosphorus contents, hematocrit reading and specific gravity (table 2).

RESULTS

A. Effect of Early Administration of Dextrose on Carbohydrate Metabolism.—1. Blood Sugar (table 4): The blood sugar contents on admission of the patients to the hospital were high, exceeding 400 mg. per hundred cubic centimeters in all but 3 cases. In the saline group, the blood sugar level fell rapidly during the first five hours from an average of 501 mg. to 146 mg. with an average dose of 91.7 units of insulin per hour. On the other hand, when dextrose was given during the first period, the level fell merely from 480 to 429 mg. with an average dose of 101.5 units of insulin per hour.

Further analysis of the 21 cases in which the patients received dextrose early reveals that the blood sugar content rose during the first period in 8, underwent no significant change in 4, showed a transitory fall and a secondary rise in 4 and fell progressively in 5. The behavior of the blood sugar depended on the clinical condition of the patient as well as on the dose of dextrose administered during the first few hours. Ten patients received dextrose at the rates of 6 to 20 Gm. per hour during the first period. A progressive fall in the blood sugar level occurred in all 3 patients with a severity index below 30 on a mean hourly dextrose intake of 13.8 Gm. and an insulin dose of 84 units. On the other hand, a progressive fall in the blood sugar level occurred in only 2 of the 7 patients with a severity index above 30 on a mean hourly dextrose intake of 13.0 Gm. and an insulin dose of 101 units. Three of the 5 patients who failed to tolerate dextrose in doses of 6 to 20 Gm. per hour were admitted in circulatory collapse. Dextrose was given during the first period at rates exceeding 20 Gm. per hour to 11 patients, including 6 with severity indexes of 30 or below. Hyperglycemia was maintained in all 11 patients, 5 showing a further rise during the first period and 3 a secondary rise after a transitory fall.

The clinical course was uneventful in the 5 patients who showed a progressive fall in the blood sugar content despite the early administration of dextrose. On the other hand, the clinical course was unfavorable in 6 of the 8 patients with increasing hyperglycemia during the first period, in 2 of the 4 patients with a maintained plateau and in 3 of the 4 patients who showed a considerable secondary rise in the blood sugar level after a transitory fall. Of the 16 patients with increasing or maintained hyperglycemia, 7 died, and 4 others went into shock from three to nine hours after the institution of treatment but subsequently recovered. For 3 of the 4 patients who went into circulatory collapse (cases 9, 19 and 22) an

utilization. Additional factors are revealed through a comparison of individual cases. For example, a study of cases 13 and 18 reveals almost identical blood sugar levels at the onset of the third period (408 and 410 mg. per hundred cubic centimeters respectively) but considerable difference in carbohydrate metabolism during the period. In case 18 the blood sugar level fell to 266 mg. despite retention of 26.9 Gm. per hour on a dose of 36 units of insulin per hour. In case 13 the blood sugar level rose to 500 mg. in the face of retention of only 10 Gm. of glucose per hour on a dose of 20 units of insulin per hour in the third period. The rise in blood sugar in case 13 would indicate that a portion of the retained glucose was not metabolized. The patient in this case was moribund at the time and well illustrates the decided carbohydrate intolerance of patients in poor clinical condition.

B. *Effect of Early Administration of Dextrose on Acidosis.*—The hourly urinalyses for acetone performed in all cases provided an index of the rate of disappearance of ketosis. The time required for the urine

TABLE 7.—*Disappearance of Acetonuria, Averages for Seventy-One Cases*

Group	Total Cases	Died While Acetonuria Was Still Present	Percentage Who Died While Acetonuria Was Still Present	Time in Which Urine Became Acetone Free, Hr.
Saline.....	22	2	9	11.5
Dextrose.....	33	6	18	11.8
Phosphate.....	16	2	13	11.9

to become acetone free averaged 12.5 hours in the saline group and 12.2 hours in the dextrose group (table 4). Furthermore, acetonuria did not disappear faster in patients who retained more than 20 Gm. of glucose per hour than in those who retained lesser quantities. Because of the absence of significant differences in this small series, observations were extended over a total of 47 patients who lived long enough to become acetone free (table 7). The time required for the urine to become acetone free averaged 11.5 hours in the 20 patients receiving saline and 11.8 hours in the 27 receiving dextrose. The groups were comparable as judged by the severity index. Therefore, the maintenance of hyperglycemia by the early administration of dextrose did not significantly alter the rate of disappearance of acetone from the urine. Reference to the carbon dioxide-combining power in table 4 offers further confirmation for the conclusion that acidosis did not disappear more rapidly in the dextrose group than in the saline group.

C. *Effect of Early Administration of Dextrose on Chloride and Water Metabolism* (tables 8 to 11).—On their admission to the hospital the saline and dextrose groups were closely comparable as to blood chloride content (485 versus 496 mg. per hundred cubic centimeters),

uneventful course would have been anticipated in view of severity indexes between 17 and 30 per cent, and in the remaining case (21) a favorable course might have been expected in view of the patient's age. The experience with these cases does not imply that the early administration of dextrose is necessarily followed by circulatory failure or a stormy clinical course, since the patients in cases 12, 17 and 18 satisfactorily tolerated equivalent or larger doses. Nevertheless, in some of the cases, particularly 9, 19, 21 and 22, there appeared to be a correlation between the admin-

TABLE 5.—*Glucose Metabolism*

Group	Case	Intake, Gm. per Hour.				Output, Gm. per Hour.				Balance, Gm. per Hour.			
		Period				Period				Period			
		1	2	3	4	1	2	3	4	1	2	3	4
Saline.....	1	0	3.1	10.9	0	2.1	0	0.3	1.2	- 2.1	+ 3.1	+10.7	- 1.2
	2	0	40.0	28.6	12.3	5.8	3.1	6.7	0.3	- 5.8	+36.9	+21.0	+12.0
	3	0	9.5	20.1	16.6	5.2	1.2	1.2	—	- 5.2	+ 8.3	+18.9	—
	4	0	0	30.8	40.0	6.7	3.2	0.7	0.5	- 6.7	- 3.2	+30.2	+39.6
	5	0	0	40.0	10.4*	2.3	0	2.8	—	- 2.3	0	+37.2	—
	6	0	—	—	—	1.4	—	—	—	- 1.4	—	—	—
	7	0	37.1	30.9	14.5	0.8	0	0.3	—	- 0.8	+37.1	+30.6	—
Average.....		0	15.0	26.9	17.4	3.5	1.2	2.0	0.6	- 3.5	+13.8	+24.9	+16.8
Dextrose.....	8	10.1	0	1.4	6.4	0	0	2.4	0.4	+10.1	0	- 1.0	+ 6.0
	9	59.2	38.9	56.4	38.8	26.8	20.4	17.6	14.1	+32.4	+18.5	+38.7	+24.6
	10	6.3	21.1	21.7	—	6.3	9.3	2.9	—	- 0.1	+11.8	+18.6	—
	11	12.5	30.0	31.3	8.3*	3.5	—	—	—	+ 9.0	—	—	—
	12	56.9	53.1	35.0	47.5	2.8	40.4	16.7	34.4	+54.1	+12.7	+18.3	+13.1
	13	20.0	0	10.3	—	4.3	1.2	0.3	—	+15.7	- 1.2	+10.0	—
	14	33.3	37.5	10.7	11.5	0.8	5.3	0.2	0.2	+32.5	+32.2	+10.5	+11.3
	15	28.8	42.5	23.1	36.3	6.8	13.1	5.3	1.3	+22.0	+29.4	+17.8	+35.0
	16	16.3	0	45.9	34.3	8.5	2.5	2.0	0.1	+ 7.8	- 2.5	+43.9	+34.2
	17	67.5	53.8	21.1	—	8.7	11.9	—	—	+58.8	+41.9	—	—
	18	50.0	75.0	42.4	8.7	17.2	31.0	15.5	1.7	+32.8	+44.0	+26.9	+ 7.0
Average.....		32.8	32.1	27.4	26.2	7.8	13.5	7.0	7.5	+25.0	+18.6	+20.4	+18.7
Phosphorus..	19	40.9	40.0	49.8	25.0	12.3	11.5	7.3	1.2	+28.6	+28.5	+42.5	+23.8
	20	28.5	25.0	—	—	10.0	6.0	—	—	+18.5	+19.0	—	—
	21	16.0	0	10.3	35.5	12.1	6.5	1.9	0.7	+ 3.9	- 6.5	+ 8.4	+34.8
	22	30.0	63.6	34.2	33.6	5.0	9.4	6.5	1.4	+25.0	+59.2	+27.7	+32.2
	23	28.5	0	37.0	4.0*	22.1	14.4	17.2	—	+ 6.4	-14.4	+19.8	—
	24	17.4	8.9	36.9	34.2	3.9	3.3	2.8	3.0	+13.5	+ 5.6	+34.1	+31.2
	25	11.8	0	40.0	49.2	6.8	2.2	0	0	+ 5.0	- 2.2	+40.0	+49.2
	26	35.2	0	41.9	—	13.6	13.1	3.9	—	+21.6	-13.1	+38.0	—
	27	12.5	49.3	34.6	25.8	4.9	7.5	7.7	1.6	+ 7.6	+41.8	+26.9	+24.2
	28	10.6	0	6.0	16.2	6.7	9.8	8.4	1.0	+ 3.9	- 9.8	+ 2.6	+15.2
Average.....		23.1	19.2	32.3	31.3	9.7	8.4	5.6	1.2	+13.4	+10.8	+26.7	+30.1

* Not included in average.

istration of dextrose during the first four hours, the maintenance of pronounced hyperglycemia and the unfavorable course.

The sharp contrast in the levels of the blood sugar in the saline and dextrose groups, which became evident in the first four to five hours, persisted throughout the rest of the study. The blood sugar content remained for the most part in the vicinity of normal in 5 of the 6 surviving patients of the saline group, even though insulin dosage was comparatively small, averaging 6.5 units per hour. On the other hand, hyperglycemia persisted throughout the entire period of observation in

TABLE 9.—Chloride Metabolism

Group	Case	Admis- sion	Plasma Chloride,† Mg./100 Cc.				Chloride Intake,† Gm. per Hr.				Chloride Output,† Gm. per Hr.				Chloride Balance,† Gm. per Hr.			
			Period				Period				Period				Period			
			1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4
Saline.....	1	543	603	585	582	591	4.09	3.07	1.19	0	0.28	0.59	0.17	0.30	+3.82	+2.48	+1.02	-0.30
	2	476	509	512	464	517	0	0	0	0*	0.04	0.02	0.05	0.01	-0.04	-0.02	-0.05	-0.01
	3	447	574	—	524	547	2.73	0.59	0	0	0.11	0.04	0.06	—	+2.62	+0.55	-0.006	—
	4	471	564	586	550	532	3.18	0.68	0.46	0	0.24	0.42	0.55	0.68	+2.94	+0.26	-0.09	-0.68
	5	474	537	597	543	603	2.04	2.73	1.46	0	0.05	0.09	0.27	0.28	+2.94	+2.64	+1.19	-0.28
	6	501	626	—	—	—	2.97	—	—	—	0.11	—	—	—	+2.88	—	—	—
	7	486	568	—	—	—	1.81	0.78	0.99	0.99*	0.11	0.19	0.80	—	+1.70	+0.59	+0.19	—
Average.....			569	570	533	568	2.40	1.31	0.68	0	0.13	0.23	0.32	0.32	+2.27	+1.08	+0.36	-0.32
Dextrose.....	8	531	546	546	555	570	2.51	0.24	0.13*	0.50*	0	0	—	—	+2.51	+0.24	—	—
	9	450	—	—	—	—	1.90	1.52	1.32	0	0.45	0.31	0.34	0.42	+1.45	+1.21	+0.98	-0.42
	10	439	579	615	615	—	2.02	1.92	1.09	—	0.08	0.18	0.05	—	+1.94	+1.74	+1.04	—
	11	—	510	538	528	507	1.36	1.82	0.68	0.91	0.14	0.88	0.57	0.38	+1.32	+0.94	+0.11	+0.53
	12	501	501	483	585	—	2.38	1.71	1.36	2.05	0.08	1.08	0.47	0.86	+2.30	+0.63	+0.89	+1.19
	13	537	507	535	—	—	2.70	0	0.62	—	0.14	0.05	0.02	—	+2.56	-0.05	+0.60	—
	14	385	471	498	506	585	2.73	4.09	1.69	0.98	0.01	0.05	0.03	0.03	+2.72	+4.04	+1.66	+0.95
	15	—	—	—	534	—	2.73	0.68	0.34	—	0.01	0.02	0.02	0.02	+2.72	+0.56	+0.32	-0.02
	16	512	581	615	604	597	2.12	2.12	0.70	0	0.05	0.05	0.19	0.05	+2.07	+2.07	+0.51	-0.05
	17	627	597	597	597	—	2.73	1.50	1.15*	—	0.20	0.49	—	—	+2.53	+1.01	—	—
	18	481	525	525	528	555	2.73	1.36	—	0	0.13	0.46	0.22	0.01	+2.60	+0.90	-0.22	-0.01
Average.....			545	564	554	567	2.36	1.54	0.87	0.56	0.12	0.32	0.21	0.25	+2.24	+1.22	+0.66	+0.31
Phosphorus.....	19	492	543	558	570	522	3.44	0	1.07	0	0.27	0.24	0.30	0.24	+3.17	-0.24	+0.77	-0.24
	20	456	558	—	—	—	3.12	2.72	—	—	0.35	0.45	—	—	+2.77	+2.27	—	—
	21	471	588	603	638	656	2.08	0	0	—	0.22	0.27	0.21	0.38	+1.81	-0.27	-0.21	-0.38
	22	634	597	585	572	572	3.28	0	0.23	0.47	0.17	0.38	0.25	0.58	+3.11	-0.38	-0.02	-0.11
	23	513	—	591	618	618	5.19	0	1.18	0.63	0.48	0.23	0.35	0.29	+4.71	-0.23	+0.83	+0.34
	24	—	556	594	586	—	2.21	0	0	0	0.23	0.26	0.17	0.12	+1.98	-0.26	-0.17	-0.12
	25	506	626	620	606	594	1.92	0	0	0	0.13	0.13	0.02	0.03	+1.79	-0.13	-0.02	-0.03
	26	534	585	597	591	—	5.33	0	0.85	—	0.76	1.45	0.23	0.18	+4.57	-1.45	+0.62	-0.28
	27	—	—	581	558	543	2.79	0.41	0	0.46	0.05	0.21	0.37	0.18	+2.74	-0.20	-0.37	+0.41
	28	498	591	621	701	646	2.04	0	0.61	0.52	0.06	0.09	0.13	0.11	+1.98	-0.09	+0.48	+0.41
Average.....			581	597	603	593	3.14	0.31	0.44	0.26	0.27	0.37	0.23	0.24	+2.87	-0.06	+0.21	+0.02

* Not included in average.

† Expressed as NaCl.

‡ Expressed as Cl.

per hundred cubic centimeters) and was nearly normal in the saline group (ranging from 111 to 163 mg. per hundred cubic centimeters). The degree of glycosuria was proportional to the blood sugar level except in the presence of shock or oliguria. Thus the early administration of dextrose maintained the blood sugar at high levels and thereby predisposed the patients to severe glycosuria.

3. Glucose Retention (tables 5 and 6): Glucose retention represents the difference between the intake and the urinary excretion. The figure for retention does not indicate the fate of the retained glucose and thus includes (1) glucose which had been oxidized, (2) that stored as glycogen and (3) that retained unchanged.

During the first period the group receiving no dextrose excreted an average of 3.5 Gm. per hour and therefore exhibited a similar negative balance. The remaining patients received an average of 28.2 Gm. per hour, of which 19.5 Gm. was retained. Since the average blood sugar level had fallen slightly in these cases, it is apparent that glucose was being oxidized or stored in the tissues at a rate approximating 20 Gm. per hour. It is noteworthy that the patients in cases 12 and 17 were retaining glucose at a maximum rate for human beings¹⁶ despite the presence of severe diabetic acidosis.

During the second, third and fourth periods, the saline group received an average of 20.5 Gm. of dextrose per hour and retained 19.2 Gm., or 94 per cent, on an average insulin dose of 6.5 units per hour, whereas the dextrose group received 28.8 Gm. per hour and retained 20.1 Gm., or only 70 per cent, on an average insulin dose of 34.1 units per hour. The saline group retained 2.6 Gm. of glucose per unit of insulin, while the dextrose group retained only 0.6 Gm. per unit of insulin. Since the question might arise as to whether the much more efficient utilization in the saline group might be explained by the smaller glucose load, attention should again be directed to the third period when the dextrose intake of the two groups was nearly equal. During this period the saline group received 26.9 Gm. and retained 24.9 Gm., or 93 per cent, on an average insulin dose of 5 units per hour, whereas the dextrose group received 27.4 Gm. and retained only 20.4 Gm., or 74 per cent, on an average insulin dose of 41 units per hour. The dextrose insulin ratio during this period was almost 5 Gm. per unit in the former and 0.5 Gm. per unit in the latter. Thus, the early administration of dextrose, by maintaining pronounced hyperglycemia and glycosuria, resulted in less efficient utilization of exogenous glucose.

The foregoing observations do not imply that the level of blood and urinary glucose is the only factor governing the efficiency of glucose

16. Woodyatt, R. T.; Sansum, W. D., and Wilder, R. M.: Prolonged and Accurately Timed Intravenous Injections of Sugar: A Preliminary Report, *J. A. M. A.* 65:2067 (Dec. 11) 1915.

presumably made up by shift of intracellular water to interstitial spaces and plasma. A rise in plasma chloride content accompanying retention of hypertonic solution will account for a portion, if not all, of the surplus chloride.

During the first period, both the saline and glucose groups showed a considerable rise in plasma chloride content while they were retaining

TABLE 10.—*Chloride Concentrations (Milligrams Per Hundred Cubic Centimeters)**

Group	Plasma	Administered Fluid	Retained Fluid
Admission			
Saline.....	304
Dextrose.....	310
Phosphorus.....	313
Period 1			
Saline.....	346	485	667
Dextrose.....	331	370	448
Phosphate.....	352	458	639
Period 2			
Saline.....	346	307	304
Dextrose.....	342	341	678
Phosphate.....	364	53†	Negative Cl balance;† positive H ₂ O balance
Period 3			
Saline.....	323	194	137
Dextrose.....	336	235	330
Phosphate.....	366	106	71
Period 4			
Saline.....	344	No Cl intake	Negative Cl balance; positive H ₂ O balance
Dextrose.....	344	175	193
Phosphate.....	360	90	9

* The concentration of chloride in the fluids was determined as follows:

(1) In "administered fluid" = $\frac{\text{Chloride (mg.) administered}}{\text{Fluid (cc.) administered}}$

(2) In "retained fluid" = $\frac{\text{Chloride (mg.) administered} - \text{chloride (mg.) excreted}}{\text{Fluid (cc.) administered} - \text{fluid (cc.) excreted}}$

† Only two patients were given chloride.

TABLE 11.—*Percentage of Excretion of Administered Fluid and Chloride*

Period	Saline Group		Dextrose Group		Phosphate Group	
	Water	Chloride	Water	Chloride	Water	Chloride
1.....	31	5	29	5	35	9
2.....	17	18	60	21	37	(119)*
3.....	25	47	45	24	30	52
4†.....	58	..	50	49	23	92

* Negative chloride balance.

† No chloride intake.

hypertonic fluid. The rise in the plasma chloride content was sufficiently great in both groups to account for the surplus chloride retained.

During the second period the saline group received and retained a slightly hypotonic solution (table 10). Since the plasma chloride content remained constant, the surplus water apparently passed into the cells. On the other hand, the dextrose group received isotonic solution

TABLE 8.—*Water Metabolism*

Group	Case	Fluid Intake, Cc. per Hr.				Fluid Output, Cc. per Hr.				Fluid Balance, Cc. per Hr.				Admis- sion	Hematocrit Reading, Vols. %				
		Period				Period				Period					Period				
		1	2	3	4	1	2	3	4	1	2	3	4		1	2	3	4	
Saline.....	1	750	563	219	0	143	78	51	151	+607	+485	+168	-151	54.3	—	47.8	44.3	48.4	
	2	182	330	236	102	200	59	121	27	-18	+271	+115	+75	58.0	—	50.5	50.9	50.9	
	3	500	324	323	165*	198	58	63	—	+302	+266	+260	—	66.6	51.8	44.2	46.5	43.7	
	4	583	125	303	330	193	145	121	126	+390	-20	+182	+204	49.6	35.3	39.3	41.3	35.4	
	5	500	600	655	86	93	35	118	77	+407	+665	+537	+9	48.3	39.2	29.4	36.0	36.4	
	6	545	—	—	—	73	—	—	—	+472	—	—	—	48.0	39.2	—	—	—	
	7	333	617	362	302	145	57	52	95	+188	+560	+310	+207	58.0	49.0	37.2	—	—	
Average.....		484	427	350	164	149	72	88	95	+335	+355	+202	+69	54.7	42.9	41.4	43.8	43.0	
Dextrose.....	8	782	133	57	157	0	0	84	6	+782	+133	-27	+151	56.8	45.0	45.5	44.2	41.3	
	9	694	491	664	393	381	262	194	197	+313	+229	+470	+196	49.0	42.0	36.0	—	—	
	10	413	458	436	—	215	277	91	—	+198	+181	+345	—	56.0	47.0	40.0	44.5	—	
	11	333	445	331	167	98	254	151	101	+235	+191	+180	+66	53.0	52.0	41.0	40.0	43.0	
	12	708	643	626	626	85	890	700	613	+683	-247	-83	+13	54.2	48.6	52.1	54.7	43.9	
	13	590	0	232	—	151	30	12	—	+439	-30	+220	—	61.5	47.7	49.0	39.8	—	
	14	917	750	357	385	17	110	50	54	+900	+640	+307	+331	58.0	41.5	44.7	45.0	35.3	
	15	708	498	215	360	194	238	128	88	+514	+200	+87	+272	48.0	42.0	40.0	42.0	42.0	
	16	420	420	483	404	180	180	60	37	+240	+240	+423	+367	58.0	48.3	41.2	44.1	38.0	
	17	760	605	321*	—	300	353	—	—	+460	+247	—	—	—	—	—	—	—	
Average.....	18	625	525	262	63	343	398	182	170	+282	+127	+80	-107	58.0	41.7	38.8	43.7	43.3	
	Average.....		637	452	366	319	179	272	166	+458	+180	+200	+101	54.7	45.6	42.8	44.2	41.0	
	Phosphorus...	19	836	830	603	206	378	345	145	123	+458	+485	+458	+83	55.7	43.2	42.1	35.3	36.5
		20	571	1,000	—	—	314	205	—	—	+257	+795	—	—	52.0	42.0	43.0	—	—
		21	480	333	201	146	185	133	44	25	+293	+200	+157	+121	58.0	45.6	43.7	40.6	36.4
		22	600	996	384	351	117	157	105	119	+183	+839	+279	+232	53.0	44.2	40.0	38.2	34.7
		23	1,000	400	590	223	394	228	258	46	+606	+172	+332	+177	49.3	35.6	40.0	35.7	34.3
		24	522	296	304	383	140	137	98	86	+382	+169	+206	+297	55.6	41.6	40.2	38.2	—
		25	353	200	330	407	137	63	15	13	+216	+137	+315	+394	47.7	45.2	37.3	35.7	32.6
		26	1,175	400	645	—	392	468	114	—	+783	-68	+531	—	47.0	36.6	37.2	35.6	—
27		875	893	443	359	195	226	217	68	+680	+672	+226	+201	63.0	—	42.0	41.3	44.6	
Average.....	28	458	479	253	244	130	163	109	61	+328	+316	+144	+183	58.7	49.3	38.9	44.0	36.9	
	Average.....		637	583	417	290	238	213	123	+449	+370	+204	+222	54.1	42.6	40.4	38.3	36.6	

* Excluded from average.

the results were analyzed in our patients with a severity index between 30 to 60 per cent. Among the 7 patients of this group who received no dextrose during the first four hours the mean severity index was 38 per cent and the fatality rate was 43 per cent. Among the 18 patients of this group who were treated with dextrose early the mean severity index was 44 per cent but the fatality rate was 67 per cent. Thus, in groups of comparable severity better results were obtained when dextrose was withheld during the first four hours than when it was administered during this period.

COMMENT

With the advent of insulin, specific treatment of diabetic acidosis became feasible. Improvement in results has followed the recognition of the need for massive doses of insulin²⁰ and for restoration of losses of sodium chloride and water.²¹ It has also been claimed that the adminis-

TABLE 12.—*Effect of Therapy on Seventy-One Successive Cases of Diabetic Acidosis*

Group	Number	Dead *	Actual Fatality Rate, %	Severity Index, %
A. Severity Index 3 to 82 per Cent				
Saline.....	22	8	36	40
Dextrose.....	33	17	52	37
Phosphate.....	16	6	37	46
Total.....	71	31	44	40
B. Severity Index 30 to 60 per cent				
Saline.....	7	3	43	38
Dextrose.....	18	12	67	44
Phosphate.....	11	3	27	44

* Three patients who died three to twenty-one days later were not considered to have died in coma.

tration of dextrose in liberal amounts during the early hours of treatment is a beneficial procedure.²² Much controversy has arisen over this state-

20. Root, H. F.: The Use of Insulin and Abuse of Glucose in the Treatment of Diabetic Coma, *J. A. M. A.* **127**:557 (March 10) 1945; correction, *ibid.* **127**:1068 (April 21) 1945.

21. Danowski, T. S.; Winkler, A. W., and Peters, J. P.: Salt Depletion, Peripheral Vascular Collapse, and the Treatment of Diabetic Acidosis, *Yale J. Biol. & Med.* **18**:405, 1946.

22. (a) Himsworth, H. P.: The Role of Glucose in the Treatment of Diabetic Intoxication, *Lancet* **2**:165, 1932. (b) Lawrence, R. D.: Treatment of Diabetic Coma, *Brit. M. J.* **2**:81, 1936. (c) Soskin, S., and Levine, R.: Carbohydrate Metabolism, Chicago, University of Chicago Press, 1946, p. 281. (d) Butler, A. M., in discussion on Diabetes Mellitus with Acidosis, Cabot Case 30451, *New England J. Med.* **231**:657, 1944. (e) Conn, J., and Bauer, J. M.: The Administration of Glucose in the Treatment of Diabetic Coma, *Univ. Hosp. Bull., Ann Arbor* **11**:49, 1945. (f) Peters, J. P.: Starvation Diabetes, *Yale J. Biol. & Med.* **17**:705, 1944; The Use of Carbohydrate in Diabetic Acidosis, *Am. J. Digest. Dis.* **13**:127, 1946.

hematocrit reading (each 54.7 per cent) and clinical degree of dehydration. During the first period the average intake and output of chloride was almost identical in the two groups (table 9). The fact that both groups retained 95 per cent of the chloride administered during this period is a reflection of the considerable chloride depletion which occurred prior to the advent of therapy. The water intake was higher in the dextrose group, but the percentage excreted during the first period was almost the same in the two groups (table 11). The volume of urine was directly proportional to the amount of glucose excreted. When values for the fluid output for the first period were plotted against those for glucose output, a straight line graph was obtained.

During the second period, the saline and dextrose groups had a comparable intake of fluid (427 versus 452 cc. per hour [table 8]) and chloride (1.31 versus 1.54 Gm. per hour [table 9]). Nevertheless, a great disparity developed between the groups in the handling of water and chloride (table 11). Water output averaged 60 per cent of the intake in the dextrose group and only 17 per cent of the intake in the saline group. The high urinary volume in the dextrose group was the direct consequence of the persistent hyperglycemia with its attendant glycosuria. In spite of the intensive diuresis in the dextrose group, a positive fluid and chloride balance was maintained, and a hemodilution comparable to that of the saline group was achieved.

The question arises of the disposition of the retained water and chloride in the two groups of cases. In the absence of measurements of plasma and interstitial and intracellular fluid volumes, indirect evidence must be utilized in the analysis of water and electrolyte retention. The following calculations are based on the generally accepted idea that chloride is almost exclusively an extracellular ion and that the concentration of chloride in interstitial fluid is the same as that in the plasma.¹⁷ When the concentration of chloride in the fluid retained during a given period and the plasma chloride level at the beginning and end of the period are known, the direction of the shift of water between intracellular and extracellular spaces may be predicted.¹⁸ For example, if the retained fluid is hypotonic in respect to chloride and the plasma chloride does not change, the surplus water presumably shifts into the cells. On the other hand, if the retained fluid is hypertonic in chloride content and the plasma level remains constant, the water deficit is

17. Darrow, D. C., and Yannett, H.: Changes in Distribution of Body Water Accompanying Increase or Decrease in Extracellular Electrolyte, *J. Clin. Investigation* **14**:226, 1935. Peters, J. P.: *Body Water*, Springfield, Ill., Charles C Thomas, Publisher, 1935, p. 132.

18. Darrow, D. C., and Yannett, H.: Changes in Distribution of Body Water Accompanying Increase or Decrease in Extracellular Electrolyte, *J. Clin. Investigation* **14**:266, 1935.

course of diabetic acidosis. On the other hand, a majority of the patients in our series had been unconscious for some time prior to their admission to the hospital. From these considerations it would appear that the condition of the patients reported on by Joslin and Root may not have been of a severity comparable to that of the patients admitted to city hospitals.

The close relationship of the condition on admission to the ultimate outcome makes a classification of initial severity a necessary preliminary to evaluation of any therapeutic regimen. Since in both Collen's series¹³ and our own practically all patients with a severity index under 30 per cent recovered whereas almost all with a severity index over 60 per cent died, regardless of the type of therapy, it would appear that only cases in the intermediate group are suitable for the evaluation of a therapeutic regimen. Eighteen of the patients in the 30 to 60 per cent severity index range received dextrose early, while 7 received no dextrose during the first four to six hours. The condition of the patients in these two groups was of comparable severity (table 11), but the fatality rate was considerably higher in those receiving dextrose during the first four hours.

The results of this study show that the early administration of dextrose and the maintenance of hyperglycemia does not have a favorable effect on the outcome of diabetic coma. While the series is not large enough for statistical significance, the trend indicates that the early administration of dextrose exerts a deleterious effect.

Considerable emphasis has been placed on restoration of carbohydrate deficit and abolition of ketosis as primary goals in the treatment of diabetic coma. Soskin has demonstrated that hyperglycemia enhances carbohydrate utilization in depancreatized animals. Contrary to expectation,²⁶ we found that comparable doses of dextrose were retained more efficiently under much smaller doses of insulin when the blood sugar level was normal than when it was considerably elevated. In our cases the maintenance of hyperglycemia by early administration of dextrose appeared to reduce the efficiency of utilization of subsequent doses. Although Conn and Bauer^{22e} attempted to demonstrate utilization of carbohydrate by patients with acidotic diabetes and hyperglycemia, their data support ours in that their 2 patients with blood sugar levels of over 400 mg. per hundred cubic centimeters on admission to the hospital retained only 8 and 30.7 per cent respectively of the dextrose administered during the first six hours of therapy. Poor retention of exogenous glucose in the presence of hyperglycemia is due in part to the limited capacity of the tubules to reabsorb glucose, a limitation which is

26. Drury, D. R., and Palmer, J. J.: Activity of Insulin in Diabetic Hyperglycemic Animals, *Proc. Soc. Exper. Biol. & Med.* **38**:394, 1938.

of chloride but retained fluid that was markedly hypertonic in respect to chloride. The high chloride concentration of the retained fluid was a consequence of the polyuria provoked by the intense glycosuria. Despite the retention of 873 cc. of fluid with a chloride concentration twice that of the plasma, the blood chloride level rose only 11 mg. per hundred cubic centimeters. The retention of so much excess chloride with so little rise in the plasma level indicated a shift of water into interstitial spaces and plasma out of cells that were already markedly dehydrated. This conclusion is borne out by the fact that the dextrose group underwent more hemodilution than the saline group during the second period even though their fluid retention was 826 cc. less.

D. Effect of the Early Administration of Dextrose on the Outcome.—Since the clinical status in diabetic coma has so important an influence on the outcome, the severity of the condition on the patient's admission to the hospital was taken as a basis for the evaluation of therapeutic results. The 7 patients of the saline group had an average severity index of 24 per cent and an actual fatality rate of 14 per cent, while the 11 patients receiving dextrose early had a severity index of 37 per cent and an actual fatality rate of 36 per cent. Inasmuch as these figures were not significant because of the small number of patients and the disparity in status on their admission to the hospital, the study was broadened to include all patients with diabetic coma admitted between July 1943 and April 1946. The series comprised a total of 71 patients. Sixteen of these received sodium phosphate and will be considered separately in another paper. For 22 of the remaining patients, from whom dextrose was withheld for at least the first four hours, the mean severity index was 40 per cent and the actual fatality rate was 36 per cent. The other 33 patients received dextrose during the first four hours and had a mean severity index of 37 per cent but a fatality rate of 52 per cent. From these averages, it would appear that the early administration of dextrose had an unfavorable effect on the outcome from diabetic coma.

An analysis of individual cases revealed that no patients with a severity index over 60 per cent survived whereas only 1 with an index below 30 per cent died.¹⁹ These figures are in accord with Collen's statistics, which revealed only two recoveries among 25 patients with an index over 60 per cent and four deaths among 28 patients with an index below 20 per cent.¹⁸ Whereas practically all patients with an index below 30 per cent recover and practically all those with an index over 60 per cent succumb, the outcome in the intervening group would be expected to reflect more closely the effect of the therapeutic regimen.¹⁸ Therefore,

19. This patient was treated with 1,000 cc. of a 5 per cent solution of dextrose subcutaneously, a procedure known to cause depletion of body electrolytes by localizing them at the site of dextrose infusion.

ingly hypertonic in chloride content and probably hypertonic in sodium as well. The lack of an appreciable rise in plasma chloride content indicated a shift of intracellular water to the extracellular spaces, which thereby caused cellular dehydration. On the other hand, the saline group in the same period retained a hypotonic chloride solution without change in plasma chloride level, thus making water available to the cells. However, during the first period the saline as well as the dextrose group retained a hypertonic chloride solution. Much if not all of the surplus chloride could be accounted for by the rise in plasma chloride content. Thus the study of chloride balance failed to reveal definite evidence of increased cellular dehydration in either group during the first period. However, Sunderman's work²⁹ would suggest that a difference in distribution of water was present in the first as well as in the second of our experimental periods. He demonstrated in diabetic patients that hyperglycemia causes the withdrawal of water from the tissue and conversely that the return of the blood sugar level to normal causes the return of water to the tissues. Hence, the falling blood sugar level in the saline group probably allowed cellular hydration to occur despite the retention of chloride as a hypertonic solution. On the other hand, the maintained hyperglycemia of the dextrose-treated patients did not permit water to go to the cells and probably promoted cellular dehydration.

It should be emphasized that patients in poor clinical condition cannot dispose of even small amounts of dextrose, as evidenced by the rising blood sugar level. It is known that under hypoxic conditions in rats utilization of dextrose is impaired and its administration causes hyperglycemia.³⁰ Hyperglycemia may complicate shock and cardiac failure in human beings independent of diabetes mellitus. Elevation of the blood sugar level in cases of shock serves only to increase the cellular dehydration already present. In such cases administration of dextrose, even in small amounts, is not advisable.

SUMMARY

For 28 patients with severe diabetic acidosis or coma determinations of the blood sugar content, carbon dioxide-combining power, chloride and inorganic phosphorus contents and hematocrit readings were made at approximately four hour intervals for twenty-four hours. Quantitative urinalyses were made in parallel periods for glucose, chloride, phosphorus and nitrogen.

The intake was accurately recorded and was limited to water, sodium chloride, dextrose and insulin, supplemented in some cases by plasma,

29. Sunderman, F. W.: Water and Electrolyte Distribution in Diabetes Mellitus, *Am. J. M. Sc.* **205**:102, 1943.

30. Van Middlesworth, L.: Glucose Ingestion During Severe Anoxia, *Am. J. Physiol.* **146**:491, 1946.

ment, and the arguments pro and con will be given before proceeding with a discussion of our results.

The arguments in favor of early administration of dextrose are based principally on animal studies showing that hyperglycemia apparently favors glucose oxidation, glycogen deposition and abolition of ketosis. Peters²³ and Butler^{22d} stated that combustion of carbohydrate is promoted by hyperglycemia. The apparent basis for this is work by Soskin showing that the depancreatized, hepatectomized animal can utilize large amounts of carbohydrate without insulin, provided that the blood sugar is maintained at high levels.¹ Mirsky²⁴ found that ketosis is diminished or abolished in depancreatized animals or in human beings with diabetic acidosis when a sufficient quantity of carbohydrate is given. These observations have been interpreted to mean that forced carbohydrate administration is beneficial in diabetic coma. Further justification for the early use of dextrose has been attempted by Soskin and Levine, who calculated a potential carbohydrate deficit of approximately 500 Gm. prior to treatment.^{22c}

Root, a leading opponent of the early use of dextrose, advised withholding it until the fourth to the sixth hour of treatment or until evidence of normal utilization of carbohydrate is present.²⁰ He moderated his strong opposition by stating that "no one supposes that in coma the administration of perhaps 10 grams per hour would be harmful, providing a sufficient amount of insulin had been given to make possible its normal utilization."²⁵ He opposed Soskin's calculations of a large carbohydrate deficit with his own figures showing a deficit of only 27 Gm. of glucose,²⁰ and urged that there has been "overemphasis of the importance of an immediate restoration of glycogen stores in the liver."²⁵

Since all authorities, including Joslin and Root, administer carbohydrate after the first four to six hours, the controversy is reduced to the question of whether the outcome is favorably influenced by the early administration of dextrose and the maintenance of hyperglycemia.

The fatality rate was extremely low in the patients treated at the New England Deaconess Hospital under a regimen of withholding dextrose until the fourth to sixth hour of treatment. Because of the excellent educational program carried on by the Joslin group and the superior intelligence and economic status of their clientele, it might be expected that their patients would come under treatment relatively early in the

23. Peters, J. P., and Van Slyke, D. D.: *Quantitative Clinical Chemistry*, ed. 2. Baltimore, Williams & Wilkins Company, 1946, p. 1109.

24. Mirsky, I. A.; Franzblau, A. N.; Nelson, N., and Nelson, W. E.: The Role of Excessive Carbohydrate Intake in the Etiology of Diabetic Coma, *J. Clin. Endocrinol.* 1:307, 1941. Footnote 2.

25. Root, H. F.: The Use of Glucose in the Treatment of Diabetic Coma, *J. Clin. Endocrinol.* 5:353, 1945.

VENTRICULAR TACHYCARDIA AND BILATERAL AMAUROSIS PRODUCED BY QUININE POISONING

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CINCHONA derivatives are being used in increasing quantities by the medical profession. Quinine has particularly widespread use as an ebolic and as an antimalarial agent. The related drug, quinidine, is gaining favor for the control of ectopic cardiac rhythms. Reports of toxicity following the overuse of quinine and its derivatives are abundant. There have been a few reports of amaurosis, with return of central vision, produced by toxic doses of quinine, and reports of the occurrence of ventricular tachycardia with overdosage of quinine have appeared in the literature; however, there is little information on the subject. The case presented here has unusual interest in that overdosage of quinine produced both ventricular tachycardia and bilateral amaurosis.

REPORT OF A CASE

J. M., a 45 year old white man, was admitted by police ambulance to Hines Veterans Administration Hospital on Dec. 29, 1946, in coma. No history was immediately available.

Physical Examination.—The patient was well developed, well nourished and slightly cyanotic. The rectal temperature was 98 F. The skin was cool and moist. The respiratory rate was 26 per minute, and respirations were shallow and rapid. He responded to painful stimulation with withdrawal movements of the extremities. There were a few old crusted excoriations about the scalp and face. The pulse was 140 and extremely feeble. Blood pressure tones were faintly perceptible—60 mm. of mercury systolic and 50 mm. diastolic. The pupils were dilated to 4 mm. in diameter, were round and equal bilaterally and did not react to light. On funduscopic examination, both disks were well outlined. The retinas were markedly pale, with maculas standing out as cherry red spots. The arterioles appeared attenuated,

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exaggerated in diabetic acidosis.²⁷ The prediction based on the work of Mirsky that early administration of dextrose and maintenance of hyperglycemia would hasten the abolition of ketosis was not borne out in our studies. Comparison of the saline and dextrose groups revealed no difference in the rate of disappearance of acetonuria.

Why should a procedure, which from the experimental work of Soskin and that of Mirsky appears to be physiologically sound, fail to accomplish its aims and even be harmful? The situation is clarified by consideration of the body as a whole. Hyperglycemia and ketosis constitute only one phase of the abnormalities in diabetic acidosis and are accompanied with striking alterations of electrolyte and water balance, with intracellular as well as extracellular dehydration and with severe disturbances of nervous, cardiovascular and renal function. Thus, the effect of any therapeutic regimen on these secondary disturbances is at least as important as its effect on the primary disturbances of carbohydrate and ketone metabolism. Soskin²⁸ has stated that physicians who do not administer liberal amounts of dextrose are like the chemist who forgets that the rate of a reaction is proportional to the concentration of the substrate. However, the purported beneficial effects of an excess glucose substrate on carbohydrate metabolism may be entirely nullified by unfavorable side effects. Our data show that these side effects are of considerable importance.

The following chain of events is set up by early administration of dextrose, which in all probability is damaging to the cells:

Glucose administration → hyperglycemia → excessive glycosuria → polyuria.

Polyuria would be expected to interfere with restoration of depleted body fluids and appeared to do so in Conn's patients. These patients received large amounts of dextrose in the first six hours and had diuresis equaling their intake. However, in our cases considerable retention of water and hemodilution occurred despite the polyuria. Hence, a further exploration of the deleterious effects of hyperglycemia and polyuria is needed. This is furnished through a comparison of water and chloride retention in our saline and dextrose groups.

A striking difference between the two groups in the handling of water and chloride became evident in the second period. The fluid intake of the dextrose group was only slightly larger than that of the saline group, but the output was nearly four times as great, largely because of an elevenfold difference in glucose output. As a consequence of the excessive glycosuria in the dextrose group, a greater proportion of the water intake than of the chloride intake was excreted. Hence, during the second period the dextrose group retained a fluid which was exceed-

27. Bjerling, T., and Iverson, P.: Zuckerschwelle und Nierenfunktion, *Acta med. Scandinav.* 82:193, 1934.

28. Soskin, S., in discussion on Root.²⁵

Because of the rapid electrocardiographic recovery, a coronary occlusion now seemed highly improbable. At this time it was evident that the electrocardiographic changes and the eyeground findings could be attributed to quinine poisoning. An attempt to secure vasodilatation by the use of vasodilators was made. Nitroscleran (sodium nitrite) intravenously and nicotinic acid orally was used, in addition to papaverine hydrochloride hypodermically.

Subsequent Course: The patient became rational and quiet on the fifth day in the hospital. On frequent reexamination, no perception of light was evidenced bilaterally. Normal color gradually returned to the retinas, but the disks became pale and the arterioles became narrowed and could not even be observed in many places. A whitish perivascular bed remained, extending from the disks peripherally

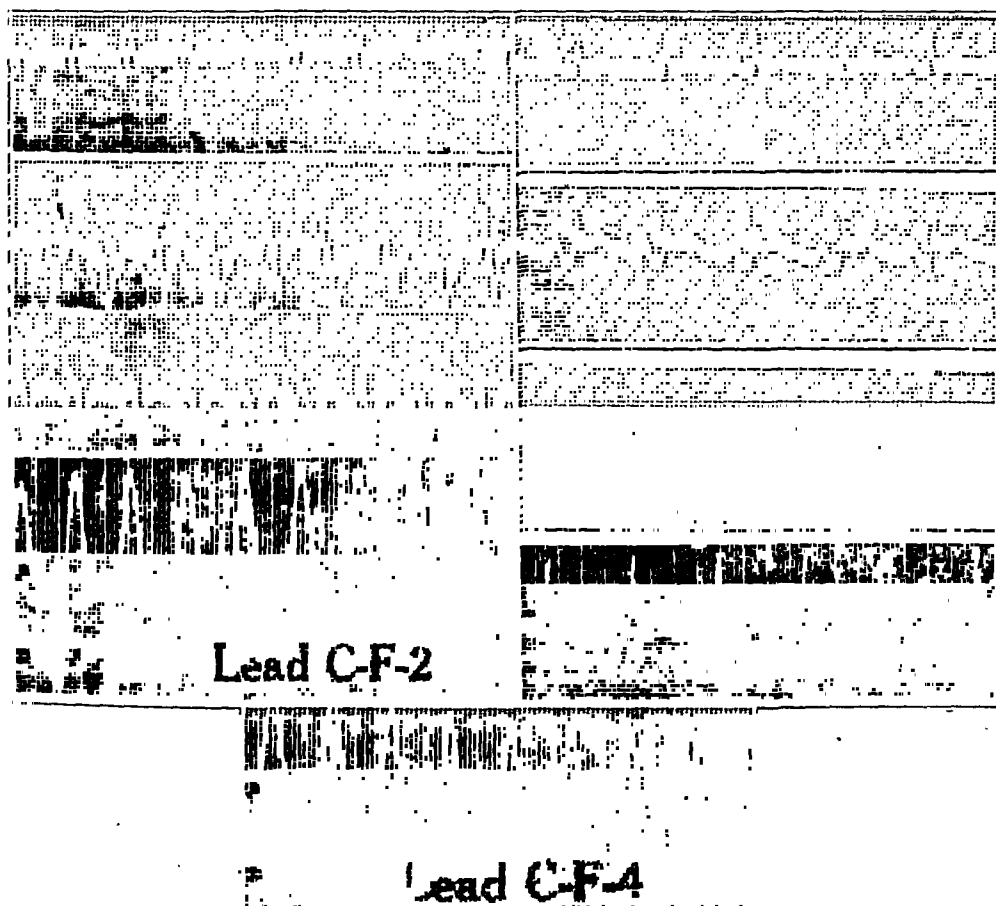


Fig. 1.—Electrocardiogram on Dec. 29, 1946, the date of the patient's admission, shows a regular tachycardia rate of approximately 140, with aberrant complexes, which was interpreted as indicating ventricular tachycardia. The tracing on the following day showed a normal sinus mechanism, with marked terminal segment changes in leads II, III and IV, which were interpreted as manifestations due to the injury currents resulting from basal infarction.

along the path of the attenuated, silver wire-appearing arteriolar trees. Six weeks after admission a central arterial blood column was present, extending peripherally one disk diameter from the optic disks. Return of light perception had then occurred. A short while later, counting of fingers at a distance of 18 inches (45 cm.) with both eyes was recorded. Light projection only could be obtained, but this was not entirely reliable. No further improvement was noted on subsequent examinations.

blood or alkali. The cases were divided into three groups according to therapeutic regimen. The first, or "saline," group received no supplementary dextrose until the blood sugar level had fallen within the normal range. The second, or "dextrose," group received dextrose from the onset of therapy. The third group was treated similarly to the second during the first four hours but subsequently received sodium phosphate intravenously, the discussion of which forms the subject of another paper.

The administration of dextrose in the early hours of therapy resulted in prolonged hyperglycemia, pronounced glycosuria and polyuria. Diabetic patients in poor clinical condition could not tolerate even small amounts of dextrose without exhibiting a rise in the blood sugar level. The amount of exogenous glucose retained per unit of insulin was much greater at normal than at high blood sugar levels. The early administration of dextrose, by maintaining hyperglycemia, diminished the efficiency of utilization of subsequent doses.

Contrary to expectation, the early administration of dextrose or the maintenance of hyperglycemia did not accelerate the disappearance of acetone from the urine or the rise in plasma carbon dioxide-combining power.

Four patients in whom an uneventful course was anticipated from their status on admission to the hospital received dextrose in large amounts during the first few hours and went into shock within three to nine hours after the onset of therapy. The early administration of dextrose appeared to have an unfavorable influence on the clinical course in these patients and on the outcome in the group as a whole. For further evidence, the clinical analysis was extended to include a total of 55 consecutive cases of diabetic coma. Thirty-three of the patients in these cases were given dextrose during the first four hours, and the other 22 received no carbohydrate during this period. Although the condition in the two groups was of comparable severity on their admission to the hospital, as judged by the index of Collen, the fatality rate was considerably higher in the patients receiving dextrose during the first four hours than in those from whom it was withheld until the blood sugar level approached normal.

The maintenance of hyperglycemia appeared to be an indirect factor in the development of shock and in the poorer clinical results obtained when dextrose was administered in the first four hours. The secondary glycosuria and polyuria resulted in the retention of chloride as hypertonic solution and therefore probably caused an abstraction of intracellular fluid and further cellular dehydration.

The results of this study indicate that dextrose should not be administered in diabetic acidosis until the blood sugar level has fallen within or near normal range.

symptom disappeared. During this additional quinine therapy, he had a continuous "buzzing" in his ears. He further stated that he had been hospitalized on three occasions at Hines Veterans Hospital for treatment of malaria.

An investigation of hospital records revealed that on each of the three hospitalizations referred to the patient had given a history of having ingested large quantities of quinine immediately prior to each admission. During all three periods in the hospital, repeated smears did not reveal the presence of malaria, and the patient at no time had an elevation of temperature. A history of alcoholism was elicited at one time. All other studies were noncontributory.

History of Present Illness.—The patient stated that he had been entirely well until two days prior to his current admission to the hospital, when he felt feverish and because of this took 45 grains (3 Gm.) of quinine. He worked that day, but on the following day, because of malaise, he took at one dose the entire contents of a box containing 100 quinine tablets. He stated that these were almost all 2 grain (0.13 Gm.) tablets but that there were a few 5 grain (0.32 Gm.) tablets. He remembered falling to the floor shortly after this and recalled nothing further until his awakening at the hospital. He denied ingestion of any alcohol during the two days prior to this episode.

COMMENT

Quinine poisoning producing both amblyopia and ventricular tachycardia has not heretofore been reported. In most recorded cases of quinine toxicity resulting in amaurosis, symptoms of involvement of the eighth nerve usually preceded the symptoms in the eyes. In this case, however, no history of impairment of the eighth nerve was elicited, but audiometric examination later revealed partial eighth nerve deafness.

The action of quinine in the retina is reported as (1) being directly toxic to the ganglion cells and (2) operating on the retinal vessels to cause extreme vasoconstriction with resulting retinal ischemia and damage. In the vast majority of reported cases of amaurosis due to quinine poisoning the patients recovered much of their vision, with only a constricted field remaining. Duke-Elder¹ stated that in all cases the tendency is toward recovery; in the milder degree of poisoning the vision may recover in a few hours, but in more severe cases amaurosis may persist for several days or even weeks, and in this event some degree of atrophy of the nerve and some permanent loss of vision are invariable. Permanent blindness, however, has not been recorded. To all intents and purposes, the patient here reported on remained blind after the ingestion of a toxic dose of quinine.

On the whole, the cardiac manifestations of quinine poisoning have been noted infrequently. Schwartz and Jezer² showed that the intravenous administration of small doses of quinine dihydrochloride did

1. Duke-Elder, S. W.: *Text Book of Ophthalmology*, St. Louis, C. V. Mosby Company, 1943, vol. 3, p. 3031.

2. Schwartz, S. P., and Jezer, A.: The Action of Quinine and Quinidine on Patients with Transient Ventricular Fibrillation, *Am. Heart J.* 9:792-801 (Aug.) 1934.

and the veins were not engorged. The ratio of arteries to veins was 1 to 4. The arterial tree could be observed only up to 3 disk diameters from the optic disk margins. The neck vessels were somewhat engorged, and there was active resistance to hyperflexion of the neck. The chest was emphysematous, with a widened anterior-posterior diameter. The lungs were hyperresonant throughout. There were transmitted gurgles and throat sounds throughout both pulmonary fields, obscuring all other auscultatory findings. The borders of the heart could not be definitely determined, and no tones were audible. The abdomen was soft. The bladder was distended to just below the umbilicus. The edge of the liver was barely palpable below the right costal arch; the borders were firm and smooth. Rectal examination revealed the prostate to be of normal size. No masses were present. The brown fecal contents did not contain any blood. Deep tendon reflexes were present and equal bilaterally, as were the abdominal and cremasteric reflexes. No pathologic reflexes were elicited.

Laboratory Procedures.—A specimen of urine obtained with a catheter contained no albumin, sugar or acetone. The red blood cell count, the percentage of hemoglobin and the hematocrit reading were normal. The white blood cell count was 21,000, with a normal differential count. An emergency portable roentgenogram of the chest revealed pulmonary congestion. Emergency chemical examination of the blood revealed the blood sugar level, carbon dioxide-combining power and nonprotein nitrogen content to be within normal limits. A spinal puncture revealed clear fluid under normal pressure, a negative Pandy reaction and the presence of 4 cells per cubic millimeter. An electrocardiogram revealed the presence of ventricular tachycardia (fig. 1).

Course in the Hospital.—First day: The patient was immediately placed in an oxygen tent, and supportive measures were instituted. Three hours after his admission the electrocardiogram was available, and because of the presence of the ventricular tachycardia, a tentative diagnosis of probable myocardial infarction was made. A sister of the patient telephoned the hospital at this time and volunteered the following information: The patient was discharged from the Navy about one year previously and had since been working as a bartender. He was separated from his wife and had been living alone in a room. He had been ill since his release from the Navy with recurrent attacks of malaria. She further stated that she had on several occasions seen the patient swallow handfuls of quinine tablets, which he seemed to keep available.

Because of the possibility that the electrocardiographic abnormalities were produced by quinine poisoning, it was decided not to use quinidine for conversion of the abnormal rhythm. The patient was placed on papaverine hydrochloride, 0.065 Gm. intramuscularly every three hours. He remained in critical condition throughout the day. His pulse rate remained at about 130 per minute, and attempts to slow or alter the rate by stimulation of the carotid sinus or by eyeball pressure were unsuccessful, as expected.

Second Day: The patient's pulse rate was 88 and regular, and the blood pressure was 110 systolic and 80 diastolic. He responded but was extremely confused. His pupils remained dilated and fixed, and he was unable to distinguish light. An electrocardiogram revealed conversion to sinus rhythm and changes suggestive of early posterior coronary infarction (fig. 2).

Third Day: The patient became delirious and thrashed about wildly. He spoke of "bottles flying past and roaches swarming." He was placed on paraldehyde and chloral hydrate for sedations. An electrocardiogram revealed that the terminal segment changes had reverted to near normal (fig. 3).

with accuracy, but the applicability to the intact human heart is open to question. The following example will illustrate the unsettled nature of this problem. The effect of the vagus is usually accepted as being that of a coronary artery constrictor. Yet most workers report that acetylcholine injected intravenously into experimental isolated dogs' hearts causes vasodilatation. Katz and Jochim,⁸ too, in their animal experiments, reported that the vagus acts as a coronary dilator.

The entire matter of vasomotor activity with reference to the coronary circulation and the mechanisms involved is not settled. There is little question that the episode of paroxysmal ventricular tachycardia in the case reported was due to the toxic effect of quinine. Whether the rhythm was initiated entirely by the direct effect of the drug on the myocardium or whether there was also an element of coronary artery constriction cannot be definitely stated. There was definite evidence that a severe degree of such vasoconstriction did occur in the retinal arteries. It seems entirely possible that vasospasm may have occurred in the coronary circulation. The experimental work previously cited does not justify such a presumption. However, these workers observed only transient effects lasting a few minutes. It seems possible that the toxic effect of quinine, producing retinal artery constriction, could similarly have caused coronary artery spasm. The electrocardiogram taken on the second day, showing a pattern indicating localized ischemia of the basal surface of the heart, further supports this possibility. The electrocardiographic pattern noted immediately after paroxysmal tachycardia usually indicates generalized myocardial ischemia due to temporary coronary insufficiency. If it is postulated that transient coronary spasm involving predominantly the basal coronary supply occurred, then localized ischemia of a degree which might give rise to electrocardiographic signs typical of the early stages of basal infarction might occur. The return of the electrocardiogram to normal was too rapid to justify a diagnosis of actual infarction. This reasoning does not justify the conclusion that coronary spasm occurred, however, since a latent sclerosis of the basal coronary vessels may have been present and the ischemia resulting from the tachycardia alone might well have been responsible for a localizing type of electrocardiographic pattern. Eisamen⁹ has reported a case of ventricular tachycardia in which the electrocardiogram, after the cessation of the arrhythmia, resembled that in basal infarction. However, the return to normal was so rapid that a temporary ischemia rather than infarction seemed to be the logical explanation.

8. Katz, L. N., and Jochim, K.: Observations on the Innervation of the Coronary Vessels of the Dog, *Am. J. Physiol.* **126**:395-401 (June) 1939.

9. Eisamen, J. L.: Electrocardiogram Simulating Posterior Myocardial Infarction After Cessation of Paroxysmal Tachycardia, *Am. Heart J.* **30**:401-410 (Oct.) 1945.

No history of involvement of the eighth nerve was elicited. The patient was able to hear a whispered voice 15 feet (4.5 M.) away with both ears. However, the audiogram revealed partial nerve deafness. There was normal hearing up to a frequency of 2,048 cycles per second and diminished hearing above this frequency, with a maximum of 70 per cent loss of hearing at a frequency of 6,000 cycles per second.

The electrocardiogram on Jan. 27, 1947, revealed no significant residual abnormalities (fig. 4).

Medical History.—When the patient had recovered from his acute symptoms, he gave the following information: No symptoms of illnesses of note antedated his military service. He was inducted on Aug. 7, 1942, and was discharged on Jan. 18, 1944, having served overseas in the Southwest Pacific from September 1942 to

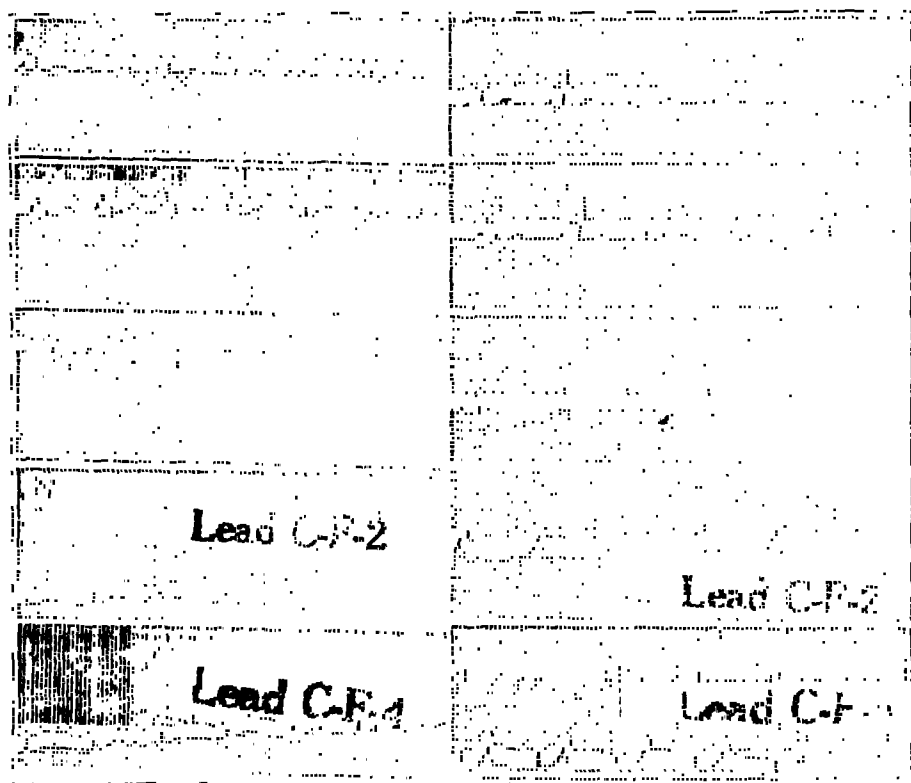


Fig. 2.—Electrocardiogram dated Jan. 1, 1947, two days later, shows a reversion of the standard leads to essentially normal configuration. Leads CF_2 and CF_4 show only notching of the T wave. The tracing on January 27 was interpreted as normal.

1943 in the Construction Battalion of the Seabees as a ship's fitter first class. The patient stated that he had four proved attacks of malaria while overseas, all treated in the sick bay with quinine. He also stated that on arrival in the States he had frequent recurrent attacks of malarial fever and was repeatedly hospitalized for the same, finally receiving a medical discharge.

Since his release from the Navy, he had been taking 15 grains (1.0 Gm.) of quinine daily. Despite this he continued to have episodes of chilly sensations occurring every fifteen to eighteen days, and, feeling that a recurrence of malaria was imminent, he would then take 45 grains (3 Gm.) of quinine daily until the

RHEUMATOID ARTHRITIS IN CHILDREN

A Clinical Study

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CHRONIC arthritis in children was first described not by Still but by Cornile¹ in 1864. In his classic thesis of 1897 Still² drew attention to the fact that in a series of 22 cases of chronic arthritis in children the disease occurred in 12 before the second dentition and was accompanied with changes in the viscera, generalized glandular adenopathy and multiple signs of systemic reaction. It is usually asserted that Still's disease is the less commonly occurring childhood manifestation of that disease or group of diseases which in adults is described as rheumatoid or atrophic arthritis. Still's observations have been confirmed by many observers, including Gibney³ in 1912, Johannsen⁴ in 1923 and Genthon in 1937.⁵ Assuming for the present that Still's disease and juvenile rheumatoid arthritis are synonymous terms, one is struck by the failure of these contributors to convey more than an incomplete survey of the clinical aspects of the disease. Influenced by the material at hand, they have inculcated in the minds of physicians a concept of a rare, unusually crippling condition, static in course and largely intractable to therapy. In 1937 Colver,⁶ at the Great Ormand Street Hospital in London, made a follow-up study of all patients hospitalized with this disease after the first World War. When examining these older patients, he was "impressed by the frequency of complete recovery and by the relative infrequency of joint crippling." This was the first rational challenge to the melancholy viewpoint of the older clinicians.

Beginning in 1941, I was given an opportunity to treat 10 children suffering from this disease.⁷ After a five year observation period, it

Dr. Richard Freyberg contributed valued assistance in the preparation of this manuscript.

1. Cornile, A.: *M. Soc. d. biol.* **1**:3, 1864.

2. Still, F. F.: *Tr. M. Soc. London* **130**:47, 1817.

3. Gibney, V. P.: *M. Rec.* **82**:93, 1912.

4. Johannsen, N.: *Acta pædiat.* **2**:354, 1923.

5. Genthon, M. J.: *Thesis, Paris*, no. 810, 1937.

6. Colver, T.: *Arch. Dis. Childhood* **12**:253, 1937.

7. By Dickson & Diveley Clinic, Kansas City, Mo., through the courtesy of Dr. Frank Dickson.

result in transient periods of ventricular fibrillation in susceptible subjects. Sokolow³ reported the occurrence of bundle branch block without other major manifestations of cinchonism following the ingestion of 10 Gm. of quinine in a 27 year old woman.

Williams and Ellis⁴ pointed out the rarity of the incidence of ventricular tachycardia from all causes. In their report of 36 cases, organic heart disease was present in 35. The tachycardia was thought to be precipitated by administration of 60 to 100 grains (4.0 to 6.7 Gm.) of quinidine in 1 of the cases.

The effect of quinine on heart muscle is qualitatively similar to that of its isomer, quinidine. One of the major effects of quinidine on heart muscle has been accepted as that of slowing which is due to the action of the drug on the refractory period of the sinoauricular node, in which it decreases the rate of impulse formation. Large doses are said to cause cardiac arrest. However, Gold, Otto and Satchwell⁵ showed that in addition to the prolongation of the QRS-T interval quinidine was also responsible for the production of sinus tachycardia. They also reported 7 instances of the precipitation of ventricular tachycardia or fibrillation after the use of quinidine in the treatment of paroxysms of auricular flutter and fibrillation.

The action of quinine on blood vessels in therapeutic dosage is that of vasodilation by direct action on the smooth muscle of the vessel wall. However, a toxic effect of quinine poisoning, that of retinal vasoconstriction, has been repeatedly reported and was observed in this case. The reported effect of the cinchona group on coronary vessels is that of vasodilatation. Kountz⁶ did not observe any effect on coronary vessels with the use of 1 cc. of a 1 to 10 solution of quinidine in a heart-lung preparation of the revived human heart; however, Elek and Katz,⁷ in experiments on isolated fibrillating dogs' hearts, reported that toxic doses of quinidine resulted in profound coronary dilatation of from 76 to 184 per cent lasting for six minutes.

The difficulty with which measurement of coronary blood flow is made is well known. Flow in isolated animal hearts can be measured

3. Sokolow, M.: Bundle Branch Block in Quinine Poisoning: Report of a Case, U. S. Nav. M. Bull. **45**:737-741 (Oct.) 1945.

4. Williams, C., and Ellis, L. B.: Ventricular Tachycardia: Analysis of Thirty-Six Cases, Arch. Int. Med. **71**:137-156 (Feb.) 1943.

5. Gold, H.; Otto, H. L., and Satchwell, H.: Use of Quinidine in Ambulatory Patients for Prevention of Paroxysms of Auricular Flutter and Fibrillation, with Especial Reference to Dosage and Effects on Intraventricular Conduction, Am. Heart J. **9**:219-237 (Dec.) 1933.

6. Kountz, W. B.: Studies on the Coronary Arteries of the Human Heart, J. Pharmacol. & Exper. Therap. **45**:65-75 (May) 1932.

7. Elek, S. R., and Katz, L. N.: Further Observations on the Action of Drugs on Coronary Vessel Caliber, J. Pharmacol. & Exper. Therap. **75**:178-182 (June) 1942.

parts of the body, notably the upper respiratory passages. In no instance did a culture of fluid from the joints yield pathogenic organisms. On the other hand, all patients admitted to the New York Hospital had cultures taken from the nose or throat and in virtually each instance pathogenic organisms (hemolytic *Staphylococcus aureus* and alpha and beta hemolytic streptococci) were demonstrated. The significance of such a finding is subject to question. Records of 20 diabetic children admitted to the same institution showed an almost equally high incidence of pathogenic organisms in the upper respiratory passages. In these circumstances there is the temptation to dismiss infection as an etiologic factor in juvenile rheumatoid arthritis, and yet in 16 of 35 children (45.7 per cent) the incidence of respiratory infection was the outstanding event in the history of the onset of disease. The following is an illustrative case.

In B. L., a previously well 10 year old girl, an acute infection of the upper respiratory tract developed, characterized by sore throat, nasal discharge, cough and elevation of temperature. The child was bedfast for three weeks during the acute stage of the illness. At the end of this time partial activity was allowed. In the fourth week of convalescence migratory polyarthralgia developed, and on admission to the hospital two months after the onset of her illness the child showed typical manifestation of rheumatoid arthritis in the hands and knees.

Hence, the question arises as to whether the presence of pathogenic organisms is more significant in the throats of children who suffer or will suffer from rheumatoid arthritis than in children who are not subject to rheumatoid arthritis or whether, to paraphrase Rich,¹¹ speaking of rheumatic fever, "the lesions of [rheumatoid arthritis] may be due not to direct action of a bacterial toxin, but may represent the effect of a hypersensitive reaction to bacterial products." Studies on the immune reactions of children suffering from rheumatoid arthritis have been reported by Boots and Coss in a series of 56 cases. Coss¹² may be quoted as follows: "The streptococcus agglutination reaction in children, taken repeatedly over a period of fourteen years, was negative in 32 of 35 cases. [The three positive reactions were subject to question.] It is our impression that positive agglutination is rare in children." Antistreptolysin titers were done in 24 cases, and, "the high median of two hundred and fifty obtained was considered to be definitely above normal,¹³ considering titers up to one hundred as normal, titers of one hundred to two hundred as suggestive of recent streptococcic infection and titers of over two hundred as being almost certain evidence of recent streptococcic infection."

With respect to the 16 cases in which a positive history of preceding infection was obtained, analysis showed certain common pathologic

11. Rich, A. R., and Gregory, J. E.: *Bull. Johns Hopkins Hosp.* **73**:239, 1943.

12. Coss, J. A., Jr.: Personal communication to the author.

13. Coss and Boots do not indicate how many of the 24 patients had high titers.

Irrespective of the exact mechanism involved, the arrhythmia presented an interesting therapeutic situation. Ordinarily, the treatment would have been prompt administration of quinidine in an attempt to induce normal sinus rhythm. Only by fortuitous circumstances was the information concerning the prior ingestion of quinine received a few minutes before quinidine therapy would have been started. It seems likely that the use of quinidine in this patient might well have caused a fatal outcome.

SUMMARY

A case report is presented of a returned serviceman who resorted to the use of large quantities of quinine in the self care and prevention of alleged malarial fever. He was admitted in coma after the oral ingestion of at least 6 Gm. of quinine sulfate.

The overdosage of quinine produced a ventricular tachycardia, with rapid electrocardiographic recovery through a stage of marked myocardial ischemia simulating early basal myocardial infarction. A persistent bilateral amaurosis also resulted from this overdosage of quinine.

A theoretic discussion of the manner in which overdosage of quinine produced ventricular tachycardia is also presented.

previously. No immediate pain or disability followed the blow, but one week later swelling, flexion deformity and mild limp developed, which persisted up to the time of his admission to the hospital, when clinical examination confirmed by roentgenologic findings showed swelling in both knees.

C. *Allergy*.—There were 2 instances of rheumatoid arthritis in children in whom allergic reactions were associated with the onset of disease. The following is an illustrative case.

TABLE 1.—*Clinical Evolution of Juvenile Rheumatoid Arthritis*

Phase	Duration	General Clinical Characteristics	Local Clinical Characteristics	Comment
Prodromal	Several days to several weeks	Severe systemic reaction; fever, malaise, tachycardia and nose-bleed	Migrating transitory polyarthritis more or less indistinguishable from rheumatic fever	Occurred in 6 of 29 New York Hospital cases
Period of extreme activity of rheumatoid process	Three months arbitrarily is the minimal time of continuous activity of primary arthritic process. Six years was the longest observed time of continuous activity of the primary arthritic process in any of these cases; it might last longer	Slight elevation of temperature; cachexia; usually presents wasting, loss of appetite, failure to gain weight; elevation of sedimentation rate	Active inflammatory reaction in joints; effusions, tenderness to palpation, warmth and muscle spasm. Redness is rare except in infants or when allergic factors are present. Pain at rest is usually absent in early months. Changes in the joints are sudden and persistent *	
Period of stabilization of rheumatoid process	Approximately 6 months †	Little or no systemic reaction; patient apparently well; sedimentation rate usually continues to be elevated; patient has no subjective complaint but remains underweight	No new joints are involved, but excess activity may provoke exacerbation; effusion without pain may persist	This is an entirely arbitrary assumption, but it is important clinically since during this period joint mobilization must be carefully watched for evidence of exacerbation
Quiescence	All subsequent time	Normal health	Complete recovery or residual joint defect, influenced further only by resultant wear and tear	If joint disease occurs at this time, it is spoken of not as exacerbation but as recrudescence

* Any joint in the body may be involved in the prodromal phase, while in the active phase the ankles, knees, hands, wrists and occasionally the elbows are involved. Synovial and cartilage involvement of the temporomandibular joints, the cervical region of the spine, the hips and the shoulders is rare in the active phase and indicates a bad prognosis.

† In 2 incompletely observed cases painless persistent effusion lasted five years in children otherwise apparently well.

L. P., a 7 year old girl, began to have attacks of difficult respiration and swelling of the face, which occurred at forty-eight hour intervals and lasted about twenty-four hours. When these attacks had persisted for several weeks she was found to react positively to most of the commonly inhaled and ingested antigens. She lost weight, and after the first month attacks were accompanied with diffuse pains in the joints. Four months following the onset of the attacks there developed persistent changes in the joints.

seemed advisable, in the light of a clinical experience which did not entirely follow that described in the literature, to review the work of other clinicians in this field.

By definition, the disease in the group of 10 cases mentioned previously and in all cases in the material taken for study fell into the category of chronic disease of the joints of children prior to puberty, nonspecific in cause, systemic in nature and characterized by persistent changes in the synovia, which in some cases but not invariably led to changes in the cartilage, ligaments and muscles of the joint involved.

Within these limits, the entire recorded clinical experience of the New York Hospital, the Hospital for Special Surgery and the New York Orthopedic Hospital was reviewed.⁸ Furthermore, for a period of six months I was granted the privilege of personally examining and following all children presenting nontraumatic effusion of the joint in the outpatient department of the Hospital for Special Surgery. To the 10 cases previously mentioned 25 cases were added from these records on a basis of having been followed by reliable observers over a continuous period of three years or more. All tabulation herein noted refers to these 35 cases.

INCIDENCE

Coss and Boots⁹ have reported the incidence of chronic arthritis in children under 12 to be 4.9 per cent of the total incidence of all rheumatoid arthritis seen in their clinic. Kuhns and Swaim¹⁰ have reported 13 cases in a series of 314 hospitalized patients (4.17 per cent). On the other hand, it is impossible to estimate accurately the incidence of the disease in the child population. That there is reason to believe that the incidence is greater than records would indicate is supported by the fact that 3 cases were recognized in the six months study period at the Hospital for Special Surgery. In normal circumstances the disease in these cases would not have been classified as rheumatoid arthritis and yet it fell within the limits of the aforementioned definition. During this period, no patients with obvious signs of the disease were admitted to the hospital. In the present series there was no indication that age or sex (21 girls, 14 boys) was a significant factor in the incidence of the disease.

PRECIPITATING FACTORS

A. *Infection*.—In this series of cases the relationship of bacterial invasion to the presence of the disease was studied by culture of material obtained from joints as well as by culture of swabs taken from other

8. The reviews were made possible through the courtesy of Dr. Samuel Levine, Dr. Philip Wilson and Dr. Alan DeForest Smith, respectively.

9. Coss, J. A., Jr., and Boots, R. H.: To be published.

10. Kuhns, J. G., and Swaim, L. T.: Disturbances of Growth in Chronic Arthritis in Children, *Am. J. Dis. Child.* 43:1118 (May, pt. 1) 1932.

in childhood and that puberty is not a satisfactory end point in time for final evaluation of the end results of rheumatoid arthritis in a child.

There does seem to be some indication that infections which may have been the precipitating factors in the original attacks are better tolerated at a later time when quiescence has been established. For example, the girl mentioned previously suffered scarlet fever at the age of 12 without recrudescence of rheumatoid arthritis.

In every instance the damaging effect of the recrudescent disease on the locomotor system has been more severe than that of the original attack.

TABLE 2.—*Severity of Rheumatoid Arthritis in Thirty-Five Cases Studied*

	Duration of Disease Process	Type of Joint Involvement	Constitutional Reaction	Associated Visceral Lesions	Residual Joint Effects	Comment
Mild	3 to 12 months	Mild synovial effusion and thickening of one knee or several small joints of the hands	Mild or absent	None	None	In a period of 6 months 3 cases were recognized at the Hospital for Special Surgery, while no case of moderate or severe degree was observed during this time
Moderate	2 to 3 years	Marked synovial effusion and thickening of the joints of the hands, knees, feet and occasionally elbows and ankles; minimal changes in the joint cartilage	Moderate loss of weight, loss of appetite, increased nervous irritability and elevation of the daily temperature 1 to 3 degrees F. in the first 6 months; elevation of sedimentation rate	None	Varies from no residual effects to moderate crippling	
Severe	6 years	Progressive destructive changes, involving many joints, including those of the cervical region of the spine, the temporomandibular joint and the shoulders	Severe cachexia; intermittent acute elevation of the temperature as high as 103 or 104 F.; high sedimentation rate	Nonspecific visceral lesions occur in about half of all cases labeled severe	Extreme deformity	The characteristic clinical feature of the severe type of disease is an inexorable and unrelentingly progressive course, with little evidence of remission at any time

PATHOLOGIC PROCESSES

Joints.—During the active stage of the disease six knees were subjected to exploration for reasons of diagnosis or treatment. The lining of the joint was found to be thickly hyperemic and edematous. Microscopic sections showed focal collection of lymphocytes and increased tissue vascularity in folds of endothelium-lined synovia (villous synovitis). There was moderate formation of pannus in 2 cases. In 1 case the lateral femoral condyle was flattened, although the articular cartilage was not eroded. These findings suggest that while the lesions

features: (1) the infection tended to be mild; (2) there was a lag period of three to ten weeks between the onset of the infection and the development of symptoms in the joints and (3) symptoms in the joints persisted for months or years following the subsidence or the disappearance of the original infection.

These findings should be contrasted with the sequence of events which is obtained when the general reaction to infection, as characterized by leukocytosis, elevation of body temperature and radial pulse rate, may be said to follow a "normal" pattern, which the following case illustrates.

J. S., a 6 year old boy, was chilled by exposure to low temperature. His shoes and feet were soaked. Three days later, pain developed in the knees, and he limped. The following day he was unable to put on his shoes because of swelling in the feet. On his admission to the hospital he complained of feeling tired and achy. His temperature on admission was 102 F., the pulse was 130 beats per minute and the respirations 24 per minute. His cheeks were bright and flushed, and the skin was hot and dry. There was a hot tender mass under the angle of the jaw on the right. The examiner noted swelling, redness and tenderness of the small joints of the hands and the feet. The total white blood cell count was 16,000. The erythrocyte sedimentation rate was 27 per minute. (Blood culture was not taken.) The child was treated by application of heat to the mass, and he was given rest and salicylates. Symptoms in the joints disappeared in twenty-four hours. The temperature and erythrocyte sedimentation rate were normal on the second day.

This child has been followed for three years and has shown no evidence of cardiac disease or disease in the joints. The characteristics of this type of clinical course are as follows: (1) the illness is acute; (2) the immune response to the illness is prompt, and (3) the development and the subsidence of abnormality in the joints corresponds chronologically to the cycle of disease in the whole body.

B. *Trauma*.—A definite history of trauma preceding the onset of disease in the joints was obtained in 7 cases, or 20 per cent. It is recognized that traumatic injury of the joints will result in a definite sequence of events in all children, that is to say, a blow in the area of a joint sufficient to cause contusion of the synovia, hemorrhage and exudation into the joint will be followed by effusion, muscle spasm and limitation of motion. The more than casual significance of trauma as a precipitating factor in rheumatoid arthritis in children may be seriously considered in those instances in which (1) the persistence of abnormality of the joints following injury is much longer than might reasonably be expected from the nature of the injury; (2) the severity of the reaction of the joint to trauma is far out of proportion to the severity of the injury or (3) pathologic features develop in joints other than those directly traumatized. The following case is illustrative.

M. M., a 6 year old boy, was brought to the hospital complaining of pain and swelling of the knees. He stated that he had been kicked in the knee one month

of the foot, hallux valgus, tailor's bunions, claw toes and overlapping toes.)

It should be stated here that the tendency in healed joints was toward increased laxity in the capsules. In the fingers in particular it was noted that deformity tended to be due to laxity of the joints and to intrinsic muscle attrition rather than to defect in the joints. A search for a consistent mode of joint progression in the cases under investigation was fruitless.

Bones.—There is a local disturbance of the calcium content of the bones adjacent to involved joints even in mild forms of juvenile rheumatoid arthritis. Whether this is due to alteration of the balance between absorption and deposition of calcium or to atrophic changes in the matrix has not been established. It should be observed, however, that no changes in the relative constituents of the serum have been consistently observed, and, what is more significant, the process of decalcification cannot be ascribed to disuse, since a return to normal function does not result in restitution of normal calcium content in the bones. Observations as late as ten years following recovery have in no instance demonstrated normal calcium content. The absence of restitution indicates a basic disturbance in the process of calcium deposition in the bones, the nature of which is not known, but which may be fundamental to the occurrence of the disease. The demineralization of the epiphyses may result in increased fragility of these structures. Crumbling and early fusion may ensue in cases of severe disease, with corresponding disturbances of growth. The subject of disturbance of growth in rheumatoid arthritis in children has been exhaustively reviewed by Kuhns and Swaim,¹⁰ who have reported 4 instances in a series of 13 cases.

Muscles.—No special studies of histologic changes in the muscles were made in the series of cases under investigation. The work of Steiner, Freund and others¹⁴ has shown that in adult rheumatoid arthritis morbid changes consisting of focal collections of monocytes and lymphocytes together with perineural cell infiltration may be consistently found. Freund¹⁵ made postmortem studies of the muscles of 2 children suffering from this disease and found changes in the muscles in no way differing from those in the muscles of adults.

Viscera.—Still,² Chauffard¹⁶ and Felty¹⁷ have drawn attention to the incidence in rheumatoid arthritis of lesions in organs other than

14. Steiner, G.; Freund, H. A.; Leichtentritt, B., and Maun, M. E.: *Am. J. Path.* **22**:103, 1946.

15. Freund, H. A.: Personal communication to the author.

16. Chauffard, A., and Ramond, F.: *Rev. de méd., Paris* **16**:345, 1896.

17. Felty, A. R.: *Bull. Johns Hopkins Hosp.* **35**:16, 1924.

COURSE AND CHARACTER OF THE DISEASE PROCESS

Consideration of a large number of cases of juvenile rheumatoid arthritis has suggested the use of certain terms to describe the chronologic cycle of the disease and to estimate its varying degrees of severity. While these terms are arbitrary, they are also purposeful inasmuch as they further clinical appraisal and aid in the adoption of rational management.

In respect to time, the cycle has been divided into four phases: prodromal, period of extreme activity, period of stabilization and period of terminal quiescence. Table 1 is a generalization of the clinical evolution of juvenile rheumatoid arthritis from its prodromal phase to its final subsidence.

In respect to severity, the disease may be classified as mild, moderate or severe, depending on the duration of the process, the degree of involvement of the joints and the nature of the constitutional reaction together with the presence of associated visceral lesions (table 2). Of 35 cases reviewed, in 11 the disease was classified as mild, in 19 as moderate and in 5 as severe. The cases of severe disease corresponded in most respects to those described by Still. The incidence of only 11 cases out of a total of 35 in which the disease was mild does not represent an accurate estimate of the relative frequency of the mild form. This is discussed in the section on incidence.

Recrudescence.—When children suffering from rheumatoid arthritis have been followed over a long period (five to fifteen years), a majority have been observed to reach a clinical state which has been described as "terminal quiescence." This is in agreement with the statement of Colver to the effect that the disease is a self-limited process. However, it was Colver's opinion that in all cases the disease became quiescent after at the most seven years and that in no case was there "recrudescence" after a quiescent period of eighteen months. This was not the experience of the patients studied, 28 of whom were observed for more than five years. Of these 28, 9 experienced a second attack of rheumatoid arthritis after periods of terminal quiescence ranging from two to eight years. In the 9 cases in which recrudescence was observed the causes appeared to be (a) infection (5 cases), (b) trauma (1 case), (c) exposure (1 case), (d) no known cause (2 cases).

In 1 instance recrudescence occurred in a boy at approximately the time of puberty and resulted in a different type of disease than that from which he had been suffering originally. This case will be described later. A second relapse occurred in a girl aged 16 years in whom the original childhood disease was experienced at the age of 6 years and reached terminal quiescence when she was 8. These cases are of extreme importance, for they indicate that puberty does not confer immunity to future disease in a person who has had an initial attack

of the central veins of the liver. Numerous areas of perivascular infiltration and one fresh vegetative lesion were found in the auricular myocardium.

CASE 2.—L. M., a 14 year old boy, has been hospitalized for nine years at St. Luke's Hospital, Kansas City. Clinical evidence of cardiac disease appeared in the eighth year of hospitalization and occurred in a period of recrudescence of disease of the joints which followed an infection of the middle ear.

In a third case autopsy was not performed, and although clinical evidence during the patient's life suggested the presence of cardiac disease, it was not sufficiently definite to support a positive diagnosis. In the records of 6 cases at the New York Hospital suspicion of cardiac disease was entertained by the attending clinicians. Dr. Harold Stewart of that institution kindly reviewed the 6 cases, and with the exception of 1 in which the possibility of rheumatic fever was not ruled out he expressed doubt as to the presence of cardiac disease in the group. In no case did the electrocardiogram show significant alteration in the conduction of the nerve impulse through the heart muscle.

One case of iritis was observed. The original ocular involvement occurred simultaneously with original lesions in the joints and impairment of vision followed. The patient had a relapse twelve years later, and acute iritis developed again in the same eye, with further reduction in vision. Four years following relapse, the disease in both the iris and the joints was completely quiescent.

In 5 of the 35 cases there was unequivocal clinical evidence of enlargement of the spleen; in 1 of these there was generalized lymphadenopathy. In 6 cases hepatomegaly was present. In these cases there was no evidence, by physical examination or laboratory study, of any factor directly responsible for the condition other than the presence of chronic passive congestion or of amyloidosis in certain fatal cases. There has been no agreement as to the significance of generalized lymphadenopathy in rheumatoid arthritis in children. To Still it was an essential feature of the disease. Colver stated that in his series of cases the aforementioned findings were commoner in patients in whom the disease began in the first four years of life. According to Colver, the presence of hepatomegaly or splenomegaly was of no prognostic significance in these cases.

It should be emphasized that with 1 exception there was clinical evidence of visceral lesions only in certain of the cases of severe disease. There was no evidence of such involvement in any of the cases of mild disease.

Psychologic Phenomena.—In addition to organic pathologic changes, there should be mention of the definite occurrence of psychic disturbance in about one third of the cases. In 7 out of 20 cases at the New York Hospital, where careful histories were obtained, there was a record of change in personality incidental to development of the dis-

in the synovia of the knees of children with rheumatoid arthritis resemble in every way those in adults, pannus formation is more limited and destruction of cartilage less severe. It is possible that there may be some correlation between the late or minimal destruction of the joint cartilage and the clinical absence of hypertrophic changes in the knees of the children studied. Table 3 summarizes the distribution of involvement of the joints in 35 cases of rheumatoid arthritis in children. In referring to this table it is to be noted that the prognosis as to function varied according to the joint involved; for example, the function of the knees was generally well restored, the elbows almost invariably lost motion but were infrequently ankylosed, involvement of the carpal joints frequently led to coalescence and the prognosis in involvement of the wrists was relatively poor. Involvement of the ankle joints

TABLE 3.—*Involvement of the Joints in Thirty-Five Cases of Rheumatoid Arthritis in Children*

	Occurrence *	Deformities During Active Stage *	Total Residual Joint Defects *	Ankylosis *
Knees.....	33	Approximately 50%	8	3
Elbows.....	15	15	14	1
Hands (metacarpals, phalangeal, interphalangeal, carpal).....	32	Not specified	11	Not specified
Wrist.....	9	9	4	1
Tarsal.....	Not specified	Not specified	..	2
Ankle.....	9	9	..	2
Temporomandibular.....	6	6	5	..
Cervical region of the spine.....	7	7	5	5
Shoulders.....	2	2	2	2
Hips.....	2	2	2	1

* Figures refer to individual joints and not to cases.

rarely led to permanent joint disturbance, and when this did occur, ankylosis was the rule. There was no instance of involvement of the dorsal or lumbar regions of the spine and no instance of involvement of the sacroiliac joints. It would seem that rheumatoid spondylitis (Marie Strümpell) does not occur in children. However, 1 of the patients studied experienced recrudescence at puberty, and in contrast to the childhood type of disease the recrudescence was characteristic of Marie Strümpell spondylitis.

J. L. (present age, 20 years) experienced the onset of rheumatoid arthritis at the age of 6, with initial involvement of one ankle and later involvement of both hands. He was free from disease of the joints from age 8 to age 15 except for one brief instance of effusion in the ankles which followed an acute respiratory infection. At the age of 15 effusion of the knees developed, and at 16 backache was first noted. Roentgenograms of the sacroiliac joints at the age of 17 demonstrated ankylosis.

Typical hypertrophic changes accompanying static defects were observed only in the feet. (These included splaying of the anterior arch

culins are administered in 1 to 100 concentration and the reactions are negative, it may be assumed that tuberculosis does not exist. Confusion arises when the reaction to tuberculin in average concentration is positive and when biopsy does not reveal the disease. In these instances there can be no answer to the diagnostic problem save that derived from serial observation over an extended period. It will then be observed that the tuberculous joint goes through a longer chronologic phase of morbid development, that quiescence of the pathologic process requires a longer period and that reactivation follows more closely on active use of the extremity. The appearance of a second involved joint may be said virtually to settle the issue in favor of rheumatoid arthritis. In the absence of positive diagnostic evidence, physicians should be cautious in proceeding to the fusion of a joint for tuberculosis.

The differentiation between two such closely related diseases as rheumatic fever and rheumatoid arthritis has not always been possible because in some cases of rheumatic fever symptoms in the joints have for a time overshadowed evidence of cardiac disease and have persisted for as long as six months. That cardiac lesions of major severity do occur in rheumatoid arthritis has already been demonstrated, and it has not been shown that the two diseases may not occur simultaneously. The diagnostic difficulty may be represented by the following case.

R. H., an 8 year old boy, complained for two years of aching in the knees and thighs. Pain was transient and not associated with fever or changes in the joints. A short systolic murmur was detected. It was heard best at the third and fourth interspaces close to the sternum. Three weeks previous to his admission to the hospital an infection of the upper respiratory tract developed, followed by a low grade elevation of temperature and fleeting pains in the wrists, fingers, knees and ankles. Examination on admission demonstrated the systolic murmur without cardiac enlargement. The blood pressure was 133 systolic and 90 diastolic and the pulse rate 80. The abdomen was normal. Consultation with arthritis service resulted in recording of the opinion that the fusiform swelling of the fingers was typical of rheumatoid arthritis. The sedimentation rate was normal, as was the blood cell count. Fluoroscopic examination of the chest and an electrocardiogram showed no evidence of cardiac abnormality. During his stay in the hospital the patient had an elevation of body temperature to 102 F. daily. He was given adequate dosage of salicylates, without appreciable effect on the disease. There was loss of weight. Three weeks after his admission erythema multiforme developed and repeated electrocardiograms showed first stage block. Three months later a typical presystolic mitral murmur developed, and eight months after the onset of disease limitation of motion and thickening of metacarpophalangeal joints was described by the attending clinician.

Study of such cases indicates that sooner or later cardiac disease becomes manifest in rheumatic fever while symptoms in the joints will obviously eventually dominate the picture of rheumatoid arthritis. During the prodromal state, the two diseases may be identical. It should be observed that the joint effusion present in rheumatic fever is

joints. Reporting recent postmortem studies, Rosenberg,¹⁸ Bennett,¹⁹ Bayles²⁰ and Portis²¹ have discussed the question as to whether such lesions represent an integral part of rheumatoid arthritis, whether they represent a series of lesions developing from a common etiologic factor or whether they are an entirely distinct coexisting disease. Rosenberg and his co-workers reported autopsies on 30 subjects who had had rheumatoid arthritis; fatal cardiac lesions were found in 10, and cardiac lesions indistinguishable from those of rheumatic fever were found in 16. This contrasts with the unreported random incidence of approximately 5 to 10 per cent of lesions considered to be characteristic of rheumatic fever in serial autopsies at the New York Hospital. It indicates that perhaps cardiac lesions occur more frequently in subjects with rheumatoid arthritis. Likewise, the high incidence of amyloidosis in rheumatoid arthritis is just beginning to be appreciated. Portis has reported 7 instances in 14 autopsies on children. It is well known that amyloidosis can be produced experimentally by repeated injections of sodium caseinate. In the German literature there are reports of amyloidosis in laboratory animals used to produce antiserums, particularly streptococcus antiserums. Moschowitz²² postulates that amyloidosis is not caused by arthritis but that the two are reactions to the same injury. Lesions of the eye, the spleen and lymphatic system, the liver, the kidneys and the colon have been discussed in the literature.

Two patients in the series of 35 studied showed positive evidence of cardiac disease during life. The assumption that cardiac disease was present was based on the observation of gross enlargement of the heart by physical and roentgenologic examination, on the presence of harsh systolic murmurs, heard loudest at the base, and on the elevation of the apical pulse rate at rest to 140 beats per minute. Both children were hospitalized for the entire duration of their illness.

CASE 1.—E. W. died at the age of 13 at St. Luke's Hospital, Kansas City, after four years of continuous hospitalization. Cardiac disease appeared in the third year of hospitalization and coincided with the development of severe destructive changes in the joints. Clinically, death was ascribed to congestive heart failure. At autopsy extreme enlargement of the liver and mild enlargement of the spleen were encountered. A sterile seropurulent exudation was present in the pericardial sac. There was thickening and retraction of the aortic valves. Senile atheromatous lesions were present in the walls of the aorta. Microscopic examination of the tissues showed chronic passive congestion of the liver and spleen, with necrosis

18. Rosenberg, E. F.; Baggenstoss, A. H., and Hench, P. S.: *Ann. Int. Med.* **20**:903, 1944.

19. Bennett, G. A.: *Ann. Int. Med.* **19**:111 (July) 1943.

20. Bayles, T. B.: *Am. J. M. Sc.* **205**:42, 1943.

21. Portis, R. B.: *Pathology of Chronic Arthritis of Children (Still's Disease)*, *Am. J. Dis. Child.* **55**:1000 (May) 1938.

22. Moschowitz, E.: *Ann. Int. Med.* **10**:73, 1931.

these children showed that almost without exception they sought treatment at more than one hospital, that periods of intensive study led to no clinical progress, that periods of extensive therapy were frequently followed by periods of no therapy at all and finally that the patients progressed through three or four different clinical specialties with no correlation or follow-up on the part of any of the persons involved. It would seem that a central agency for the purpose of classifying and following all cases of rheumatic disease in children in a given community would prove of immense value.

2. *Rest*.—The fundamental feature of any program of treatment of rheumatoid arthritis in children is rest. The study of approximately 50 cases has shown no instance of exacerbation during the active phase of the disease in any child hospitalized and given complete rest over a period of thirty days or more. In no instance has the incidental disuse of the involved extremities resulted in further loss of previously restricted motion in the joints. On the contrary, the records show that all too frequently improvement led to early abandonment of rest, with deleterious effects. There were 6 well documented instances of exacerbation of the disease while the patient was under direct institutional observation as a consequence of too early mobilization. Under prolonged rest each child showed subjective improvement and natural inclination to increased activity of the joints.

The use of rest must be clarified and defined. It means absolute rest in bed, but it does not mean mummification of the patient or his parts. Limited exercise may be carried on. Active motion of the joints will more or less depend on the pain involved in carrying out movement. In a broad way, it will be occupational or diversionary in contradistinction to supervised physical therapy, because the latter tends to be too vigorous. Two instances occurred in which physical therapy resulted in definite exacerbation during hospitalization, 1 as a result of weight-bearing exercises and 1 following pool therapy. Measures effective in adults do not necessarily apply to children. Inasmuch as ankylosis does not usually occur and motion is regained without intervention, the need for physical therapy is less urgent. The one deleterious effect which has been observed to follow prolonged immobilization is the destruction of the femoropatellar cartilage resulting from persistent extension of the knee. On the whole, it must be realized that in the face of advancing disease neither forced active motion nor passive manipulation, in or out of the water, will serve to stave off the increasing muscle spasm; the less the involved joints are disturbed in children, the sooner function will be regained.

To obtain rest, simple orthopedic measures are a useful adjunct in the active phase. When the muscles of the knees, for example, demonstrate spasm and motion is painful, a simple Buck's extension

ease. The changes consisted in aberrations of mood and personality, fear complexes and hyperirritability, which were not characteristic of the child prior to the onset of the disease and which disappeared when the child regained normal health. Two children were subjected to extensive psychometric examination and were adjudged to be of low intelligence level. I was able to examine 1 of these patients eight years after her acute illness. She at present holds a steady though menial job in the hospital and is considered to be a good worker. She has progressed through three forms of high school. The second patient was recently passed by Selective Service. One of the patients in the present series made two suicidal attempts. At present, three years later, he is a fairly stable person.

DIAGNOSIS

Diagnosis in this disease is frequently erroneous. It is seldom established in the early stages. The four mistakes commonly made are as follows:

1. The mild attack may be passed over entirely as a minor traumatic incident or labeled under such descriptive terms as toxic, nonspecific or villous synovitis.
2. Rheumatoid arthritis in children frequently exists as a monarticular disease, and in overlooking this clinicians tend to misdiagnose the disease, calling it tuberculosis.
3. It is frequently impossible in one examination to distinguish between rheumatoid arthritis and rheumatic fever.
4. In the absence of definite substantiating evidence there is a tendency to dismiss the cases as instances of brucellosis, syphilis or gonorrhea.

The outstanding diagnostic error in the management of rheumatoid arthritis consists in the confusion of the monarticular form with tuberculosis. This error was made no less than seven times in the 35 cases studied. Two patients were subjected to surgical treatment in these circumstances. Monarticular onset occurred in 15 patients, usually in the knees. Extension to other joints was the rule in these patients, but there was not infrequently a lag of two to four years before other joints became involved. Unfortunately the synovitis of tuberculosis may closely resemble that of rheumatoid arthritis, and in cases in which tuberculosis is actually present in the joint the biopsy specimen may not contain bacilli or tubercles. Significant demineralization of the epiphysis may result in marginal pitting or erosion, which is indistinguishable by roentgenologic examination from that of tuberculosis. Analysis of aspirated fluid from the joint is not helpful, since the cell count and the chemical constituents of the fluid may be altered in the same manner and degree in the two types of disease. If tuber-

resulted in ankylosis. In 1 case the patient was subjected to synovectomy at a time when there was active arthritis of about equal severity in the two knees. The knee operated on yielded the poorer result. The other two synovectomies were carried out on the same child at a time of quiescence of the arthritic disease. Fairly good motion was obtained but was useless since the child was unable to walk for other reasons. Certainly the results of surgical intervention carried out during the active stage of the disease have not been encouraging. Whether reconstruction is feasible after several years of quiescence has not yet been demonstrated, although recent experience in this field has been encouraging. This will form the basis of a future report.

6. *Medical Treatment.*—There are no reports of the controlled use of salicylates in the treatment of rheumatoid arthritis in children. Chrysotherapy in children has been extensively reported by Coss and Boots. Coss is quoted:

In a series of 51 cases 22 were treated with gold and 29 by [other] methods. Fifty-three per cent [of gold-treated patients] showed moderate to marked improvement [as compared with] 75 per cent of the non-gold-treated patients [showing improvement]. This suggests that gold . . . is . . . ineffective. Actually the gold-treated patients were those with very active disease in whom all other treatment methods failed. We [still] feel that a trial of gold is indicated after a reasonable period of time [six to twelve months] . . . in the event of failure to secure clinical improvement with other methods.

Coss observed toxic reactions to the drug in 10 of the 22 children receiving chrysotherapy. The reactions were of mild degree in all save 1 patient, in whom toxic hepatitis was reported to have developed.

RESULTS

In 35 cases the end results were as follows: 1. Three patients died, the cause of death being (a) amyloidosis, (b) undetermined and (c) congestive heart failure. 2. Seven patients were left with severe residual crippling, 2 were moderately crippled, 2 were minimally crippled and 14 recovered without residual crippling. 3. In 7 patients the disease was still active at the time of last observation, and of these, 2 were severely crippled, 4 moderately crippled and 1 minimally crippled.²⁴

Table 4 presents the end results in this series compared with those reported by Colver.

24. Severe crippling means either practical or utter impairment of locomotion or loss of the use of an upper extremity, moderate crippling means major derangement of a major joint without loss of function of the limb involved, i. e., ankylosis of the elbow in a good functional position, and minimal crippling means major impairment of a minor joint or minor impairment of a major joint.

transient, lasting only a few days. This is followed by a brief period of stiffness and sometimes itching. The redness of the joint seen in rheumatic fever is rarely observed in rheumatoid arthritis. Clinical experience supports the assertion that a child suffering from rheumatic fever will frequently exhibit elevation of body temperature without appearing to be notably sick, whereas the child with fever in rheumatoid arthritis is obviously extremely ill.

Diagnosis in the mild form of rheumatoid arthritis must rest positively on the persistence of effusion in the joints and negatively on the exclusion of other diagnostic possibilities. It must be appreciated, for example, that mechanical factors such as prolonged immobilization of an extremity in plaster may be followed by mild swelling of the joints. Heavy children with retarded epiphysial centers frequently complain of aching in the joints in the weight-bearing extremities. On the negative side, there is no available evidence to suggest either that such conditions as brucellosis actually produce objective changes in joints or that syphilitic or gonorrheal arthritis in children is a reasonable diagnostic possibility. This question was pursued in the record libraries of the three hospitals previously mentioned, in addition to which access was had to the records of the Bellevue Hospital, New York.²³ At the Hospital for Special Surgery there is record of a Charcot joint (hip) occurring in a boy of 15 years. This is the youngest patient in whom syphilis of the joint was demonstrated. Study was made of all children at the aforementioned hospitals in whom a diagnosis of gonorrhea was made. Although gonorrheal vaginitis and gonorrheal conjunctivitis are not uncommon, there were no proved cases of gonorrheal arthritis. In 1 instance, in which gram-negative diplococci considered to be characteristic of gonorrhea were cultured in a smear from the urethra of an 8 year old girl admitted to Bellevue Hospital, there was coexistence of acute arthritis of the elbow. This inflammatory process in the joint subsided after two weeks. There was no aspiration and no follow-up.

TREATMENT

The conditions under which this material has been gathered make it impossible to compare results obtained from different means of treatment or to evaluate any single therapeutic approach; however, it is possible to outline several broad features which should be included in any plan of management of rheumatoid arthritis in children.

1. *Adequate Care and Follow-Up.*—Clinical responsibility for children with rheumatoid arthritis must not be shifted from department to department, and follow-up must be adequate. Attempts to trace

23. Access was possible through the courtesy of Dr. Otto Steinbrocker.

Of the 35 patients, 14, or 40 per cent, are completely well. Some of the 14 have reached adult life. Of those reaching adult life, 2 have experienced recrudescence after puberty. These two occurrences would indicate that although any individual "attack" of rheumatoid arthritis may be said to be quiescent, the arthritic "status" persists even in the absence of any arthritis. In this sense, a "cure" of the attack may have been accomplished, but the potential abnormal reaction of any of these predisposed persons to some future injury is not altered. In regard to adult function of the joints of children in whom permanent damage has resulted, it may be anticipated that secondary degenerative changes will sooner or later be imposed on the original inflammatory process, and this will be in direct proportion to the extent of the original destruction and to the mechanical activity of the particular joint involved.

With reference to treatment of rheumatoid arthritis in children, this paper has argued for no particular scheme of management save rest. On the contrary, it has attempted to demonstrate the course of the disease irrespective of therapy on the basis of which any specific progress might be evaluated. It is readily seen that such an evaluation must take into consideration the chronicity of the disease plus the fact that if the patient is seen early there is no means of foretelling when the disease will naturally react violently and progressively and when it will subside regardless of treatment. Successful treatment must be gaged by the following criteria: (1) shortening of the duration of active inflammation, (2) control of spread to previously uninvolved joints and (3) prevention of relapse in the quiescent period.

SUMMARY

The records of some 200 children suffering from rheumatoid arthritis have been studied.

Thirty-five cases have been followed for sufficiently long periods to enable study of the end results. Etiologic factors in these cases appear to have been (1) infection, (2) trauma and (3) allergy. The essential feature of the disease is an altered specific reaction of the patient to these activating agents.

There is essential agreement with the conclusion of Colver that the disease is self limited. There is essential disagreement with the same author in regard to the "second attack" or recrudescence after quiescence.

Study of the results obtained after the involvement of various joints by the rheumatoid process indicates a wide difference in the outcome to be anticipated according to the joint involved, being poorest in the elbows, the carpal joints and the wrists and relatively good in the ankles and the knees.

Visceral lesions accompany the severe forms of the disease, the lesions of greatest importance being "rheumatism-like" lesions in the heart and

will relieve sign and symptom. Of all plaster apparatus, the most useful is the cock-up splint applied to the wrist to obtain relaxation of the long extensor muscles. It must be applied in a position of comfort, and increased dorsiflexion will be gained by repeated application.

Braces must be used logically and purposefully. It is an old orthopedic adage that braces will not straighten a crooked limb, nor will the brace modify the deleterious effects of exercise if weight-bearing activity is basically harmful. When a child is ready to walk by reason of quiescence of his disease, he will not require a brace except for the support of a joint whose ligaments have been found to be relaxed in consequence of the disease. A light Goldthwaite type of brace has been found to be useful when applied to the backs of children in whom serious postural defects have developed in consequence of general muscular disability. This is used in conjunction with postural training and it is in answer to this aspect of the problem that physical therapy has been found to be most useful.

3. *Manipulation*.—Six patients in this series were subjected to forceful manipulations of joints, some of them repeatedly. In none was there any evidence of permanent gain in the direction of normal alignment or motion. On the contrary, the records indicate that following such treatment deformity reoccurred on release of pressure. The significance of trauma has been pointed out, and forceful manipulation can only be regarded as a traumatizing procedure.

4. *Focal Infection*.—There is no basis for fear in the attack on focal infection during the active phase as distinguished from the prodromal phase of the disease. Ten patients were subjected to surgical treatment of the upper respiratory passages during the active stage of the disease, without exacerbation of arthritis. On the other hand, in 5 cases the disease was originally precipitated by such treatment. It should be added that the outcome in the 5 cases was good. In regard to focal infection, the outcome of the arthritic disease in general was best in cases in which no focal infection existed. It was poorest when focal infection was unsuccessfully or repeatedly treated or when there was more than one single incident of focal infection.

5. *Surgical Procedure*.—Major operative treatment was attempted in 6 instances in this series. In 2 cases the knee joints were surgically fused. Examination of the synovia at operation indicated in both cases that active inflammation was present. Within a period of four months following operation acute exacerbation of the arthritic process developed in the 2 children involved. The causal relationship of the flare-up to the operative attack is debatable, but the crippling which ensued did render the reconstructive procedures useless to the patient. Synovectomies of the knees have been attempted four times in this series. One

ACUTE PANARTERITIS IN ALLERGIC PERSONS

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THE ROLE of hypersensitivity in acute arterial disease has been emphasized by Rich.¹ We have recently seen 2 patients with acute arteritis, and both had definite atopy. In 1 the arterial disease was not diagnosed until the necropsy was performed. In the other, who had an acute angiitis accompanied with severe exacerbation of an allergic dermatitis, the diagnosis was made during life, recovery probably being favored by the demonstration of the underlying pathologic process. In addition to the theoretic interest, therefore, it is hoped that an increasing awareness of this syndrome will have practical applications in clinical diagnosis and treatment.

REPORT OF CASES

CASE 1.²—J. K., a 40 year old white farmer, was seen in the dermatology department in April 1946. He complained of perianal itching of two years' duration and a pruritic eruption around the perineum of nine months' duration. Scratch tests and a test diet showed that he was sensitive to eggs, and he improved on an egg-free diet plus roentgen therapy of the cutaneous lesions. Five months later he inadvertently ate some cake containing eggs and suffered an acute exacerbation of the perineal lesion, followed by severe conjunctival edema and congestion. Two days later there appeared a red papular rash on the thighs, and this soon became generalized. He was hospitalized in another city and improved after local therapy and some medication, the nature of which is unknown. One week after returning to work, however, he had another exacerbation and was admitted to our hospital.

From the Departments of Pathology and Medicine, the Marshfield Clinic and St. Joseph's Hospital.

1. (a) Rich, A. R.: The Role of Hypersensitivity in Periarthritis Nodosa, *Bull. Johns Hopkins Hosp.* **71**:123, 1942; Additional Evidence of the Role of Hypersensitivity in the Etiology of Periarthritis Nodosa, *ibid.* **71**:375, 1942; (b) Hypersensitivity to Iodine as a Cause of Periarthritis Nodosa, *ibid.* **77**:43, 1945. (c) Rich, A. R., and Gregory, J. E.: The Experimental Demonstration That Periarthritis Nodosa Is a Manifestation of Hypersensitivity, *ibid.* **72**:65, 1943. (d) Rich, A. R., and Follis, R. H., Jr.: Studies on the Site of Sensitivity in the Arthus Phenomenon, *Bull. Johns Hopkins Hosp.* **66**:106, 1940. (e) Rich, A. R.: The Role of Hypersensitivity in the Pathogenesis of Rheumatic Fever and Periarthritis Nodosa, *Proc. Inst. Med. Chicago* **15**:270, 1945.

2. This case was used through the courtesy of Dr. Stephan Epstein.

COMMENT

Further study of rheumatoid arthritis in children may modify the conclusions which have been based on only 35 cases; yet there is the feeling that the survey has been sufficiently broad to justify the working concept which has been presented.

The mechanical aspects of the disease have been presented in some detail because study of the records has indicated that perhaps pediatricians and rheumatologists have not been sufficiently tolerant of the fact that rheumatoid arthritis is a systemic disease which primarily involves the locomotor system.

Coss and Boots observed the disease in patients younger than those in the cases reported in this paper. The differences are not irreconcilable.

TABLE 4.—*End Results in the Cases Studied as Compared with Those in Colver's Cases*

	(1) Colver	(2) Present Series	Composite (1 + 2)
Number of cases.....	49	35	84
Dead.....	12 (24.5%) (2 from streptococcal septicemia, 1 from amyloid, 1 from uri- nary infection, 1 from pericarditis and 7 from unknown causes)	3 (8.6%) (1 from unknown causes, 1 from amyloid and 1 from congestive failure)	15 (17.8%)
Inactive.....	19 (38.8%)	25 (74.3%)	44 (52.3%)
Severely crippled.....	2 (4%) (unable to earn livelihood)	7 (14.3%)	9 (10.7%)
Moderately crippled.....	6 (12.2%)	2 (5.7%)	8 (9.6%)
Mildly crippled.....	4 (8.1%)	2 (5.7%)	6 (5.2%)
Completely recovered.....	7 (14.3%)	14 (40%)	21 (20%)
Active.....	18 (38.7%)	7 (20%)	25 (27.7%)
Severely crippled *.....	..	4	
Moderately crippled *.....	..	2	
Mildly crippled *.....	..	1	

* Data in relation to this were not tabulated for Colver's cases.

The material in this paper which was taken from the New York Hospital closely follows that of Colver and of Coss. In a children's medical service acute forms of the disease in young children are more frequently encountered. However, such material is in itself incomplete, since it does not take cognizance of the many cases of mild disease nor does it embrace the considerable number of partially crippled children who are treated in the orthopedic units.

Of the 35 cases available for study of the end results, only 5 might be said to come within the category of so-called Still's disease by virtue of conformation to the original description of Still's cases. It would seem preferable to consider chronic nonspecific disease of the joints in children as rheumatoid arthritis, realizing that in a small number of cases the disease is severe, deforming and accompanied with visceral lesions.

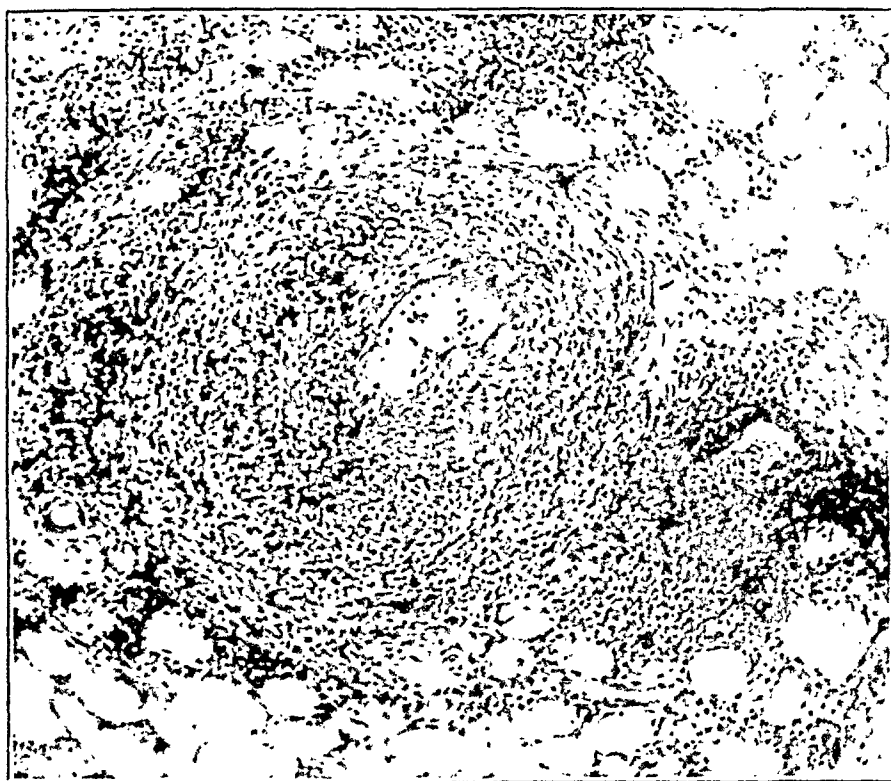


Fig. 1 (case 1).—Photomicrograph showing the acute arteritis in a mesenteric arteriole. Hematoxylin and eosin stain; $\times 70$.

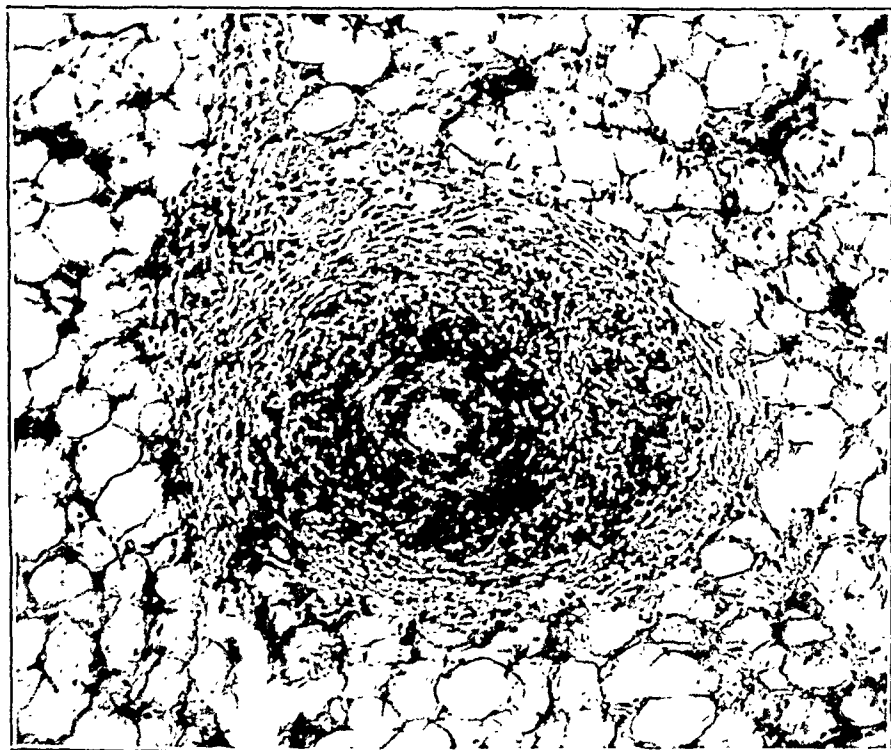


Fig. 2 (case 2).—An arteriole in the periadrenal fat. Hematoxylin and eosin stain; $\times 70$.

amyloid degeneration in the liver and spleen. Clinical evidence of cardiac disease is present in some of the most severe cases.

A persisting monarticular form of rheumatoid arthritis in children may be sometimes observed and is difficult to distinguish in some cases from tuberculous synovitis. Rheumatoid arthritis and rheumatic fever may closely resemble one another.

There is a reasonably good basis for the removal of focal infection during the active phase of the disease. Surgical attack on joints during the active phase of the disease has not been followed by sufficiently good results in the cases studied to make it an advisable undertaking.

The incidence of recovery is in truth high if all cases are taken into consideration.

Previous to August 1946 he had been seen many times in the dermatology department because of severe asthma and allergic dermatitis. The past history was otherwise noncontributory. No familial history of allergy was obtained.

Physical examination on admission revealed no abnormalities. The blood pressure was 150 systolic and 90 diastolic. The patient did not appear ill.

Laboratory Findings.—On admission of the patient to the hospital the urine showed a specific gravity of 1.015, and the highest reading ever obtained was 1.019. The albumin content was 200 mg. per hundred cubic centimeters, and the sediment contained leukocytes, red blood cells and many casts of the hyaline, waxy, vacuolated and granular type. These findings persisted. A modified Mosenthal renal function showed severe renal damage. The blood on admission showed a hemoglobin content of 11.7 mg. per hundred cubic centimeters, a red blood cell count of 4,660,000 and a white blood cell count of 16,700, with 84 per cent segmented cells, 12 per cent lymphocytes, 2 per cent eosinophils and 2 per cent monocytes. The nonprotein nitrogen content was 35 mg. per hundred cubic centimeters. The total plasma protein was 5.7 Gm. per hundred cubic centimeters. Later there was a progressive drop in blood hemoglobin and in the red blood cell count and hypoproteinemia which reached a level of 3.98 Gm. per hundred cubic centimeters. Examination of the stool, gastric analysis and roentgenologic studies revealed nothing significant.

Course in Hospital.—The course was progressively downhill. The temperature rose to 101 to 103 F. The hypoproteinemia became severe in spite of the intravenous administration of large quantities of plasma. The patient complained persistently of abdominal pain, and distention was severe. Terminally he became disoriented, showed signs of decompensation and had a few mild convulsive seizures. He died one month after his admission to the hospital.

Autopsy.—A complete necropsy was performed, but only the main findings are given. The chief lesion was a generalized panarteritis (figs. 2 and 3), most severe in the lungs, liver, pancreas, adrenals, kidneys and prostate. Histologically the arterioles showed more involvement than the large arteries. There was extensive cellular infiltration, not only around the vessels but also into the media and intima. Lymphocytes and large mononuclear cells were predominant, with a few plasma cells and eosinophils. There was fibrinoid necrosis of the arteriolar walls, with destruction of the elastic laminae. The vascular necrosis was most severe in the kidneys and liver. One of the branches of the hepatic artery contained a completely organized thrombus, while many of the other vessels contained fresh thrombi.

Final Anatomic Diagnosis.—The final anatomic diagnosis was: visceral angiitis (panarteritis, periarteritis nodosa), glomerulonephritis on the basis of visceral angiitis, pleural adhesions, hydrothorax, ascites, fibrous obliterative pericarditis, passive congestion of the lungs, spleen and liver and moderate generalized arteriosclerosis in a patient who had had a history of atopy.

COMMENT

Many theories have been advanced as to the cause of periarteritis nodosa, recent evidence favoring the concept that it is the result of hypersensitivity. This theory was first suggested by Gruber in 1923,³ but at that time there was little to support it. In 1937 Clark and Kaplan⁴

3. Gruber, G. B.: Zur Frage der Periarteritis nodosa, mit besonderer Berücksichtigung der Gallenblasen- und Nieren-Beteiligung, Virchows Arch. f. path. Anat. 258:441, 1923.

4. Clark, E., and Kaplan, B. I.: Endocardial, Arterial and Other Mesenchymal Alterations Associated with Serum Disease in Man, Arch. Path. 24:458 (Oct.) 1937.

The family history revealed that two sisters had eczema, while a third had severe urticaria when she ate strawberries.

Physical examination revealed nothing noteworthy except for the generalized subacute dermatitis. The blood pressure was 150 systolic and 80 diastolic. The laboratory findings were entirely normal.

Course in Hospital.—Under a regimen of local therapy, administration of tripelennamine hydrochloride and an egg-free diet, the dermatitis improved. However, four days after his admission to the hospital the patient began to complain of abdominal distention and nausea. This was followed by vomiting and generalized pain in the upper abdominal area. At this time the white blood cell count had risen to 25,900 per cubic millimeter. On physical examination the picture was that of an acute abdominal condition, and exploratory laparotomy was advised.

At operation the only abnormality found was a moderately inflamed appendix, which was removed. Pathologic examination showed a subacute appendicitis.

The patient was given routine postoperative care. On the second postoperative day his temperature rose to 99.6 F. and there was a recurrence of the abdominal pain and nausea. The next day he had severe crampy abdominal pain, vomiting and three loose stools consisting of thin, reddish brown foul fluid. The fluid gave a strongly positive reaction for blood by the benzidine test, as did the vomitus. The urine, which had previously been normal, now contained 400 mg. of albumin per hundred cubic centimeters, with many leukocytes and red blood cells in the sediment as well as many waxy, cellular and granular casts.

On the seventh postoperative day the sutures were removed, and that afternoon the wound suddenly disrupted with evisceration. The peritoneal cavity contained a large amount of brownish fluid. About 3 feet (0.9 meter) of ileum was found to be indurated and in part gangrenous. This was resected.

Pathologic Examination.—The specimen examined consisted of 80 cm. of small bowel. The wall was indurated and thickened in a patchy fashion. In these areas the mucosa was essentially normal except for marked hyperemia. Microscopically there was focal gangrene of the wall. The striking lesion was widespread necrosis of the arterioles in the mesentery and in the bowel wall (fig. 1). These showed massive infiltration into all coats, with a pleomorphic cellular exudate composed chiefly of polymorphonuclear cells. There were only a few eosinophils. The media showed varying degrees of necrosis. Many of the arterioles were occluded by recent thrombi.

The pathologic diagnosis was focal gangrene of the ileum on the basis of visceral angiitis.

Postoperative Course.—The postoperative course was uneventful. The dermatitis gradually disappeared, but the urine continued to show definite abnormalities. One month after operation the amount of albumin in the urine was 30 mg. per hundred cubic centimeters, with leukocytes, red blood cells and casts of many types in the sediment. Three months later a phenolsulfonphthalein test of renal function showed a 55 per cent total excretion of dye. Up to the time of the writing of this article there has been no elevation of the blood pressure.

Comment.—The gangrene of the bowel in this patient with acute allergic dermatitis was thought to be on the basis of an acute arteritis. The evidence of acute renal damage coincident with the abdominal condition, plus the residual renal damage, leads us to suppose that there was simultaneous arterial involvement in the kidneys and possibly in other organs.

CASE 2.—F. G., a 67 year old white farmer, was first seen in August 1946, with a chief complaint of pain in the chest and abdomen. Eight months previously he

The occurrence of prodromal infection is common in periarteritis nodosa,¹⁰ and this focuses attention on the role of bacterial allergy. Peale and others¹¹ reported a case of periarteritis nodosa complicating scarlet fever, and it is noteworthy that in addition their patient had a history of allergy as evidenced by the appearance of hives following the eating of tomatoes. Metz¹² produced the lesions experimentally with foreign protein and streptococci, and Gerber¹³ succeeded in producing arterial necrosis by repeated intravenous administration of bacterial filtrates. Masugi and Isibasi¹⁴ did the same by sensitization with bacteria.

Attempts to produce experimental hypersensitivity to the sulfonamide drugs have failed, probably because the antigen involved is a sulfonamide-plasma protein combination.¹⁵ Nevertheless, many of the studies on anatomic lesions due to damage caused by sulfonamide compounds¹⁶ indicate the frequent occurrence of arterial lesions in instances of such damage.

It seems, therefore, that a variety of antigens may be responsible, provided that the "soil," about which little is known, is predisposed to react by showing vascular damage. Indeed, vascular disease in the broad sense is still poorly understood. Arterial lesions in certain clinical syndromes are anatomically so similar that it has properly been suggested that the term "visceral angiitis" be used for the whole group. The suspicion has frequently been expressed that there is a basic factor common to rheumatic fever, periarteritis nodosa, anaphylactoid purpura, lupus erythematosus, scleroderma, dermatomyositis and glomerulonephritis.¹⁷ These conditions are of course less common than vascular

10. Spiegel, R.: Clinical Aspects of Periarteritis Nodosa, *Arch. Int. Med.* **58**:993 (Dec.) 1936.

11. Peale, A. R.; Gildersleeve, N., and Lucchesi, P. F.: Periarteritis Nodosa Complicating Scarlet Fever, *Am. J. Dis. Child.* **72**:310 (Sept.) 1946.

12. Metz, W.: Die geweblichen Reaktionserscheinungen an der Gefäßwand bei hyperergischen Zuständen und deren Beziehungen zur Periarteritis nodosa, *Beitr. z. path. Anat. u. z. allg. Path.* **88**:17, 1932.

13. Gerber, I. E.: The Schwartzman Phenomenon in the Kidneys of Rabbits: Observations on Effects of Intravenous Administration of Bacterial Filtrates, *Arch. Path.* **21**:776 (June) 1936.

14. Masugi, M., and Isibasi, T.: Ueber allergische Vorgänge bei Allgemeininfektion vom Standpunkt der experimentellen Forschung, *Beitr. z. path. Anat. u. z. allg. Path.* **96**:391, 1936.

15. Schönholzer, G.: Die Bindung von Prontosil und die Bluteiweiskörper, *Klin. Wchnschr.* **19**:790, 1940.

16. Black-Schaffer, B.: Pathology of Anaphylaxis Due to Sulfonamide Drugs, *Arch. Path.* **39**:301 (May) 1945.

17. Banks, B. M.: Is There a Common Denominator in Scleroderma, Dermatomyositis, Disseminated Lupus Erythematosus, the Libman-Sacks Syndrome and Polyarteritis Nodosa? *New England J. Med.* **225**:433, 1941. Klemperer, P.; Pollack, A. D., and Baehr, G.: Pathology of Disseminated Lupus Erythematosus, *Arch. Path.* **32**:569 (Oct.) 1941. Rich.^{1e}

had had pneumonia, which had been treated with one of the sulfonamide compounds. He recovered fully and felt well until March 1946, when he began to feel weak, nervous and mentally depressed and noted severe anorexia. In May 1946 he began

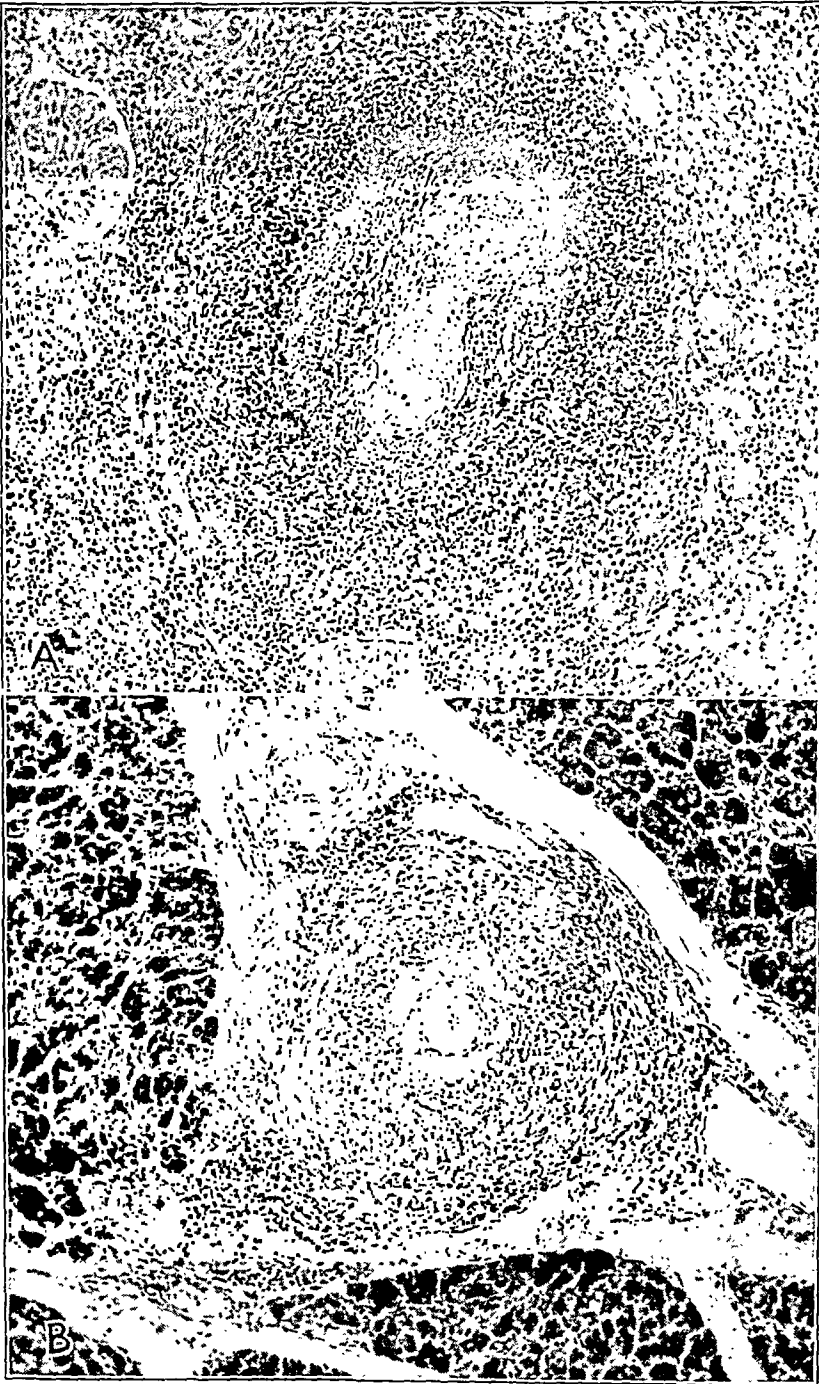


Fig. 3 (case 2).—*A*, kidney; the fibrinoid necrosis in the media is striking, and there is recent thrombosis. *B*, pancreas. Hematoxylin and eosin stain; $\times 70$.

to have severe abdominal pain. There was a total loss of weight of about 30 pounds (13.6 Kg.) in six months.

Progress in Internal Medicine

SYPHILIS

A Review of the Recent Literature

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AND

JOSEPH EARLE MOORE, M.D.

BALTIMORE

(Continued from Page 690)

Bismuth Preparations.—Eagle¹⁰⁶ has studied the toxicity and therapeutic efficacy in experimental syphilis in rabbits of three representative bismuth compounds—sodium and potassium bismuthotartrate (“bismosol”), serving as a prototype of the water-soluble bismuth compounds, a-carboxyethyl-b-methyl-bismuthononoate (“biliposol”), representative of fat-soluble compounds, and bismuth subsalicylate in oil, the preparation which has been most widely used in the treatment of syphilis. All these three preparations were given intramuscularly, a single injection being given approximately six weeks after intratesticular inoculation.

The results indicate that all three types of bismuth preparations studied are, mol for mol, from one half to two thirds as active therapeutically as is oxophenarsine hydrochloride similarly administered in a single injection in the treatment of experimental syphilis in rabbits. By virtue of their lower toxicity, two of the compounds, bismuth subsalicylate in oil and biliposol, provided margins of safety between the effective and toxic levels from six to eight times greater than that provided by oxophenarsine hydrochloride.

Voss and Tatum¹⁰⁷ present experimental data suggesting that in rats paraaminobenzoic acid exerts a low grade protection against the toxic action of such bismuth preparations as sodium bismuthyl citrate, sodium bismuthyl mannonate and sodium bismuthyl tartrate.

Bismuth Gingivostomatitis.—The prevention of gingivostomatitis during administration of bismuth is discussed by Scopp.¹⁰⁸ In this

106. Eagle, H.: The Relative Toxicity and Therapeutic Activity in Experimental Syphilis of Bismuth Subsalsalicylate, Bismosol and Biliposol, *Am. J. Syph., Gonorr. & Ven. Dis.* **30**:549 (Nov.) 1946.

107. Voss, E., and Tatum, A. L.: Protective Action of *p*-Aminobenzoic Acid Against Certain Bismuth Preparations, *J. Pharmacol. & Exper. Therap.* **90**:161 (June) 1947.

108. Scopp, I. W.: Bismuth Gingivo Stomatitis, *Mil. Surgeon* **99**:196 (Sept.) 1946.

reported the observance at autopsy of lesions similar to periarteritis in 2 patients who had received serum therapy for lobar pneumonia and in whom serum sickness had developed shortly before death. These authors were reluctant to point to a causal relationship between the serum sickness and the arterial lesions. Eason and Carpenter,⁵ also in 1937, in a paper on the treatment of rheumatic fever with antiscarlatinal serum, reported that in 1 of the treated patients in whom death followed serum sickness the lesions of periarteritis nodosa were found at autopsy. They felt that in the presence of rheumatic infection it was difficult to relate the vascular lesions to the serum sickness.

More recently, Rich^{1a, b} has brought forth some definite evidence that these arterial lesions are related to hypersensitivity. He has not only reported the occurrence of panarteritis in 7 persons treated with serum and sulfonamide compounds, but has also stated that in 1 case a biopsy taken before serum sickness appeared showed no arterial lesions while tissues studied after did show typical arteritis. Rich and Gregory^{1c} later succeeded in producing the lesions in rabbits made hypersensitive to horse serum.

With these observations in mind, corollary evidence is not difficult to find. For example, it is generally accepted that the pathologic process in the Arthus phenomenon is primarily that of vascular damage⁶ and that the changes in the vessel wall, from the early edema to the terminal necrosis, can also be found in periarteritis nodosa if cases are studied in which the disease is of different duration. Also, many observers have noted that significantly more persons with asthma succumb to periarteritis nodosa than would be expected.⁷ In 1943 Reimann⁸ reported periarteritis nodosa in 2 cases of trichinosis, significant in view of the high degree of hypersensitivity produced by the antigen in this disease. Necrotizing arteritis has also been reported in a fatal case of Loeffler's syndrome⁹ and in an instance of hypersensitivity to iodine.^{1b}

5. Eason, J., and Carpenter, G.: Treatment of Acute Rheumatic Polyarthritits with Concentrated Antiscarlatinal Serum, *Quart. J. Med.* **30**:93, 1937.

6. Gerlach, W.: Studien über hyperergische Entzündung, *Virchows Arch. f. path. Anat.* **247**:294, 1923. Rich and Follis.^{1d}

7. Rackemann, F. H., and Greene, J. D.: Periarteritis Nodosa and Asthma, *Tr. A. Am. Physicians* **54**:112, 1939. Kline, B. S., and Young, A. M.: Cases of Reversible and Irreversible Allergic Inflammation, *J. Allergy* **6**:258, 1935. Kallos, P., and Kallos-Deffner, L.: Die experimentellen Grundlagen der Erkennung und Behandlung der allergischen Krankheiten, *Ergebn. d. Hyg., Bakt., Immunitätsforsch. u. exper. Therap.* **19**:178, 1937.

8. Reimann, H. A.; Price, A. H., and Herbut, P. A.: Trichinosis and Periarteritis Nodosa, *J. A. M. A.* **122**:274 (May 29) 1943.

9. Bayley, E. C.; Lindberg, D. O. N., and Baggenstoss, A. H.: Loeffler's Syndrome: Report of a Case with Pathologic Examination of the Lungs, *Arch. Path.* **40**:376 (June) 1945.

Arsenical Encephalopathy: Prebble¹¹² has made an extensive review of the subject of arsenical encephalopathy and has reported 187 cases, more than the total previously reported.

Of 75 cases described in the literature, 57 were fatal. The onset of symptoms occurred after a varying number of arsenical injections but most often early, i. e., after the second or third injections. The commonest history was found to be as follows:

Intense headache is the initial symptom and may be accompanied by fever, shivering and vomiting. On the following day the patient suddenly has an epileptiform convulsion, with clonic spasms, followed by unconsciousness. The deep reflexes are lost; a positive Babinski's sign is present; squint and various other signs indicative of involvement of the central nervous system may occur. Retention of urine is common. Epileptiform convulsions recur at intervals, and coma continues until death. A fatal result often supervenes within 48 hours of the onset of symptoms.

The exact incidence of arsenical encephalopathy is unknown. It is obviously, from this author's large series, more frequent among patients treated in India. It has been observed with greater frequency since the introduction of massive arsenotherapy. Here it has occurred in 1 in every 113 patients treated, and the incidence of fatal cases has been 1 in every 268. Several writers have noted that pregnancy apparently adds to the risk of this reaction.

The several theories of causation are discussed. The author is inclined to the view that individual idiosyncrasy is a possible but unsatisfactory explanation. He favors rather the theory indicating a direct toxic action of arsenicals on the capillaries of the brain, stressing pathologic evidences of damage to the structures and noting that the arsenic content of the brain may be higher in patients with encephalopathy than in those who have been similarly treated but who die from other causes.

Treatment of the reaction is unsatisfactory. The most useful remedies are thought to be morphine, epinephrine hydrochloride and glucose in isotonic solution of sodium chloride. Vitamin B and oxygen are suggested as being of value. In this author's experience, 2,3-dimercaptopropanol (BAL) appeared to have little influence on the condition. Because bronchopneumonia is a frequent complication, it is considered to be important to nurse comatose patients in the Fowler position.

Agranulocytosis: Eleven cases in which agranulocytosis occurred during intensive arsenotherapy for syphilis are reported by Fisher,

112. Prebble, E. E.: Arsenical Encephalopathy: A Review of the Literature with a Report of a Further One Hundred and Eighty-Seven Cases, *Brit. J. Ven. Dis.* 22:93 (Sept.); 139 (Dec.) 1946.

disease of a "degenerative" nature, but whether or not arteriosclerosis is truly degenerative remains to be proved. Perhaps the evidence presented by Holman ¹⁸ for a dietary factor in the production of necrotizing arteritis in dogs will help to bridge this gap.

In any case, there is now enough evidence to show that the relationship between hypersensitivity and acute arterial disease is more than accidental. We feel confident that more and more of these cases will be recognized before autopsy is performed. In our case 1 all medication was stopped as soon as the diagnosis was made, in the hope that the antigen might be excluded by such means. This may be a life-saving measure when the antigen is exogenous. It is to be hoped that new developments in the field of the antiallergic drugs will lead to a more active method of therapy in the near future.

SUMMARY

Two cases of acute necrotizing arteritis in persons with atopy have been observed. In 1 case the condition was diagnosed early in the course of the illness, all medication stopped and a good recovery made.

The importance of the role of hypersensitivity in acute arterial disease is emphasized, and the possible clinical implications are discussed.

18. Holman, R. L.: Acute Necrotizing Arteritis, Aortitis, and Auriculitis Following Uranium Nitrate Injury in Dogs with Altered Plasma Proteins, *Amer. J. Path.* **17**:359, 1941; Necrotizing Arteritis in Dogs Related to Diet and Renal Insufficiency: V. Evidence for a Dietary Factor, *ibid.* **19**:977 (Nov.) 1943.

intravenous drip method and the less practicable prolonged schedules used previously, was used during the earlier years of World War II and ultimately was replaced by penicillin therapy.

From an analysis of 3,000 patients with primary or secondary syphilis treated by this twenty-six week schedule, Sternberg and Leifer¹¹⁶ report that the results in terms of therapeutic effectiveness were "excellent." Of the 2,976 whose status could be appraised, 95.36 per cent had made "satisfactory progress." An apparently favorable outcome was observed in 98.3 per cent of the primary cases in which there was seronegativity, in 94.5 per cent of the primary cases in which there was seropositivity and in 89.3 per cent of the cases of secondary syphilis. A total of 138 patients (4.6 per cent) manifested some form of relapse or reinfection or had positive or doubtful reactions to serologic tests for syphilis at the final examination and were therefore considered to have failed to respond to treatment. There were but 18 (0.64 per cent) in whom the cerebrospinal fluid was abnormal among the 2,842 examined.

In general, the twenty-six week treatment was tolerated well. It is estimated that with this form of therapy in the Army there was 1 death for 33,000 patients treated. There were no deaths from treatment of the 3,000 patients in the reported series, and in only 2 instances was it necessary to abandon arsenical therapy because of untoward reactions.

When a survey was made to determine the regularity with which the twenty-six week treatment was being given in the European Theater, it was found that only about 38 per cent of the patients treated were completing the course of therapy within less than eight months. Accordingly, a trial of a more intensified scheme of arsenobismuth therapy, compressed into a period of twenty days, was undertaken.

Pillsbury and Loveman,¹¹⁷ who have analyzed the results with this twenty day schedule in a series of 1,343 patients with early and early latent syphilis, conclude that the method yielded "very satisfactory one-year results . . . in terms of achievement of a negative serologic test for syphilis and a negative cerebrospinal fluid." Of the cases followed for one year or more, over-all satisfactory results were obtained in 94.96 per cent, unsatisfactory results in 4.26 per cent and "pending" results in 0.78 per cent.

A total of slightly over 4,000 patients with early syphilis received therapy by this method, and there were no resultant deaths. Approximately 96 per cent of the patients completed the outlined course of

116. Sternberg, T. H., and Leifer, W.: The Treatment of Early Syphilis by the Twenty-Six-Week Mapharsen-Bismuth Schedule, *Am. J. Syph., Gonorr. & Ven. Dis.* **31**:124 (March) 1947.

117. Pillsbury, D. M., and Loveman, A. B.: Six to Twelve Month Follow-Up Results in Early Syphilis Treated by a Twenty-Day Intensive Arsenobismuth System, *Am. J. Syph., Gonorr. & Ven. Dis.* **31**:115 (March) 1947.

dentist's experience, the bismuth line rarely occurs when there is good oral hygiene. Bismuth is deposited when there is vascular stasis and is especially common in the presence of gingivitis, tartar or pyorrhea pockets.

Arsenical Preparations.—Dichlorophenarsine hydrochloride (3-amino-4-hydroxyphenyldichloroarsine hydrochloride), an arsenoxide which in solution yields phenarsine oxide ("mapharsen") has been established as a safe and therapeutically effective arsenical. Beerman and Wammock¹⁰⁹ report that the buffer which is added to dichlorophenarsine hydrochloride may be a factor in the low toxicity of this preparation. These workers suggest that the addition of sodium ascorbate somewhat lessens its toxicity without decreasing therapeutic effectiveness.

Tryparsamide: From a comprehensive review of the use of tryparsamide in syphilotherapy, Koteen¹¹⁰ concludes:

1. Because pharmacologic studies show that pentavalent arsenicals, including tryparsamide, are not therapeutically effective until reduced to the trivalent form and do not possess greater penetrability or affinity for the central nervous system than the trivalent drugs, one cannot expect that tryparsamide will be an effective chemotherapeutic agent for the treatment of syphilis.

2. Tryparsamide often causes permanent visual damage in spite of detailed precautionary measures. This is especially true in patients with *tabes dorsalis*.

3. Considerable variation in the therapeutic results attributable to tryparsamide is evident throughout many reports. Patients with neurosyphilis treated in this clinic failed to substantiate the reported therapeutic efficacy of the drug.

4. There are alternative methods for treating all forms of neurosyphilis in which tryparsamide is said to be of value, and none of these regimens is as dangerous as one employing tryparsamide.

Toxic Effects of Arsenical Compounds.—The most recent compilation of the United States Navy statistics regarding reactions to arsenicals has been made by Burton, Justyn and Anderson.¹¹¹ After the administration of 1,394,868 doses of neoarsphenamine (1925 to 1945) there were 55 deaths, mostly due to hemorrhagic encephalitis and exfoliative dermatitis, a ratio of 1 death to every 35,361 injections. After 1,115,873 injections of oxophenarsine hydrochloride (1935 to 1945) there were 7 deaths, a ratio of 1 death to every 159,410 injections.

109. Beerman, H., and Wammock, V. S.: Dichlorophenarsine Hydrochloride in the Treatment of Syphilis, *Am. J. Syph., Gonorr. & Ven. Dis.* **31**:150 (March) 1947.

110. Koteen, H.: The Present Status of Tryparsamide in Syphilotherapy, *Am. J. M. Sc.* **213**:611 (May) 1947.

111. Burton, O. L.; Justyn, G. W., and Anderson, L. T.: Toxic Effects of Arsenical Compounds as Employed in the Treatment of Syphilis in the United States Navy, 1945, *U. S. Nav. M. Bull.* **47**:180 (Jan.-Feb.) 1947.

tiveness) circumscribe its general use. Metal chemotherapy continues to be widely used, not only for those treated on an ambulatory basis but as an adjunct to decrease the not inconsiderable number of failures resulting from the use of penicillin alone.

There has also been concern with the lethal effects of arsenic, not in its relation to the treatment of syphilis but as a component of that most feared of war gases, lewisite. In 1939, as part of a program of war research in Peters' laboratory at Oxford, there were initiated investigations which led to the demonstration of the effectiveness of dithiols against the noxious action of arsenic. The study has since been actively pursued in England and in this country.

There is now considerable evidence that the toxicity of arsenicals is related to their ability to combine with essential sulfhydryl groups of certain tissue proteins and thus to block physiologic systems vital to cellular economy. Protection against this action of arsenic may be afforded by compounds containing a competing dithiol capable of forming a ring compound at least as stable as the compound of arsenical with tissue sulfhydryl groups. This fact led to the preparation and testing of several dithiols, one of which, 2,3-dimercaptopropanol (British anti-lewisite, or BAL), has proved highly efficacious not only against lewisite and arsenical compounds used in syphilotherapy but also against the baneful actions of other heavy metals.

Information concerning 2,3-dimercaptopropanol was carefully restricted throughout the war. With the cessation of hostilities, it became possible to publish the accumulated data. A committee composed of representatives of the various groups which had participated in the wartime study of BAL has presented, as a symposium on the dithiols, selected papers of fundamental value. Those dealing with biochemistry have been published in the *British Biochemical Journal*,¹²⁰ those relating to toxicology, pharmacology and experimental therapeutics in the *Journal of Pharmacology and Experimental Therapeutics*¹²¹ and those concerned with clinical applications in the *Journal of Clinical Investigation*.¹²² Abstracts of the articles in this symposium of greatest interest to syphilotherapists appear in a recent issue¹²³ of the *American Journal of Syphilis, Gonorrhea and Venereal Diseases*.

120. Stocken, L. A., and Thompson, R. H. S.: British Anti-Lewisite: I. Arsenic Derivatives of Thiol Proteins, *Biochem. J.* **40**:529, 1946; II. Dithiol Compounds as Antidotes for Arsenic, *ibid.* **40**:535, 1946; III. Arsenic and Thiol Excretion in Animals After Treatment of Lewisite Burns, *ibid.* **40**:548, 1946.

121. Symposium on the Pharmacology of Dithiols, *J. Pharmacol. & Exper. Therap. (supp.)* **87**:1 (Aug.) 1946.

122. Symposium on Clinical Uses of 2,3-Dimercaptopropanol (BAL), *J. Clin. Investigation* **25**:451 (July) 1946.

123. Symposium on BAL, abstracted, *Am. J. Syph., Gonorr. & Ven. Dis.* **31**: 93 (Jan.) 1947.

Holley and Fein.¹¹³ In all cases the reaction occurred toward the end of the scheduled course of treatment. Prompt cessation of arsenical administration and therapy with dimercaprol, "pentnucleotide," liver extract and, in the more severe cases, blood transfusions sufficed to prevent mortality. The importance of careful observation of patients receiving intensive arsenotherapy is emphasized, regulation of body temperature and routine leukocyte counts being considered especially desirable. In 50 per cent of the patients described, agranulocytosis occurred after there had been a febrile reaction of the "ninth day erythema" type.

The Milian Reaction: An extensive review of the reaction commonly referred to as "the ninth day erythema of Milian" has been made by Binazzi,¹¹⁴ who reports ninety-one such reactions. The reaction is thought to be an expression of an anaphylactic state of intolerance to the arsenical drugs accompanied with imbalance of the autonomic nervous system. In this author's experience, the Milian reaction occurred more frequently in women than in men and most often in patients with early syphilis under arsenical treatment for the first time. The concomitant administration of sulfonamide compounds appeared to increase the incidence. The author stresses the constitutional manifestations—anorexia, nausea, vomiting, headache, sore throat, lymphadenopathy, conjunctival suffusion, pruritis, musculoskeletal pains and fever. He recommends that antisyphilitic therapy be suspended for twenty to forty days and that at the end of this time arsenotherapy be resumed with great caution.

The Jarisch-Herxheimer Reaction: Giberti¹¹⁵ reports that in a patient with an endourethral chancre acute urinary retention developed forty-eight hours after the institution of antisyphilitic therapy with an arsenical and bismuth. He attributes this complication to a Jarisch-Herxheimer reaction.

Semi-Intensive Arsenobismuth Therapy of Early Syphilis.—In July 1942 the United States Army, acting on the recommendation of the Subcommittee on Venereal Diseases of the National Research Council, adopted for routine use a schedule for treating early and latent syphilis with the administration of forty injections of oxophenarsine hydrochloride and sixteen of bismuth subsalicylate in a period of twenty-six weeks. This schedule, a compromise between the more toxic five day

113. Fisher, S.; Holley, H. L., and Fein, G.: Agranulocytosis: Report of Twelve Cases in Which It Followed Intensive Arsenotherapy for Syphilis, *Arch. Dermat. & Syph.* **55**:57 (Jan.) 1947.

114. Binazzi, M.: Contributo alla conoscenza della sindrome del IX giorno (eritema del IX giorno di Milian), *Gior. ital. dermat. e sif.* **87**:458 (Dec.) 1946.

115. Giberti, A. Z.: Ritenzione acuta da reazione di Herxheimer in portatore di sifiloma iniziale endourethrale, *Arch. ital. dermat., sif. e vener.* **19**:138, 1946.

from twenty-four to seventy-two hours, and all were well in eight days. Because this compilation is self-limited, it is difficult to assess the role of BAL.

7. In five of fourteen patients with so-called arsenical jaundice, the administration of BAL in relatively small doses was followed by symptomatic improvement. In three of those five patients this was shown to be associated with a prompt fall in the blood bilirubin level. In seven of the patients, however, there was either no effect or improvement was so slow that it could not be causally related to the BAL. The effect in the remaining two patients was debatable.

8. BAL had no therapeutic effect in three patients with aplastic anemia or in two patients with dermatoses following prolonged administration of Fowler's solution.

9. The administration of BAL was followed by an increased urinary excretion of arsenic in eleven patients with exfoliative dermatitis treated with BAL. The similar results in six normal subjects, and in twelve men given BAL from six to seventy-eight hours after the inhalation of minute amounts of an arsenical smoke, will be described in a later paper. The results in six patients with jaundice were, however, equivocal in that only two of the six showed a significantly increased excretion.

10. The dosage of BAL in the patients so far treated has averaged from 500 to 700 mg. in the first twenty-four hours and a total of from 1,000 to 1,500 mg. over a period of from three to seven days. In no patient has there been a serious systemic toxic reaction referable to BAL. In view of that fact, the encouraging therapeutic results obtained to date and the desirability of more intensive treatment, it is suggested that the unit dosage and the number of injections be increased in the serious manifestations of arsenical poisoning.

Toxicity of 2,3-Dimercaptopropanol.—The drug 2,3-dimercaptopropanol is itself toxic, but the margin of safety between the effective and the toxic level is large enough to make its use clinically feasible. Administered intramuscularly in peanut oil and benzyl benzoate, injections of 3 mg. per kilogram (average adult dose of 150 to 200 mg. or 1.5 to 2.0 cc. of a 10 per cent solution) may be repeated every four hours during the first forty-eight hours and once or twice daily thereafter until recovery is complete.

Cameron, Burgess and Trenwith¹²⁶ have sought by means of experiments on rabbits and rats to find out whether untoward effects may arise from the use of 2,3-dimercaptopropanol in conditions of impaired function of the kidneys and liver. Renal tubular damage was produced with uranium acetate, and carbon tetrachloride was used to damage the liver. When the drug was injected into animals with severe renal disease, no evidence of toxic effects greater than those in normal animals was obtained. With hepatic damage, however, there was enhanced toxicity. The authors suggest that care should be exercised when the drug is given to patients suspected of having impaired hepatic func-

126. Cameron, G. R.; Burgess, F., and Trenwith, V. S.: The Possibility of Toxic Effects from 2,3-Dimercaptopropanol in Conditions of Impaired Renal or Hepatic Function, *Brit. J. Pharmacol.* 2:59 (March) 1947.

therapy. A more detailed report of the untoward reactions encountered during the course of the twenty day schedule of arsenobismuth therapy has been made by Cormia and Blauner.¹¹⁸ It is apparent from their report that although there were no deaths this intensive schedule is inherently toxic. Among 500 patients untoward reactions of various kinds (cerebral irritation, jaundice, toxic erythema, agranulocytosis, excessive fever, hemorrhagic encephalitis and persistent albuminuria) necessitated the termination of therapy in 4.8 per cent of those treated.

Massive Arsenotherapy for Prenatal Syphilis.—Curtis and Morrow¹¹⁹ have found massive arsenotherapy a rapid and highly efficient method for the treatment of early syphilis associated with pregnancy. Forty women with syphilis were treated by the intensive intravenous drip of 1,080 to 1,200 mg. of oxophenarsine hydrochloride over periods of five to eight days. In addition, each patient received 260 to 520 mg. of bismuth subsalicylate in oil intramuscularly. Nine patients were treated in the first trimester of pregnancy, 21 in the second trimester and 10 in the third. Thirty-three infants born of these mothers were kept under observation for at least three months, and all were nonsyphilitic. Five could not be followed. Three infants died; none, however, had any evidence of congenital syphilis. Two women who became pregnant a second time after intensive therapy were not retreated and gave birth to normal nonsyphilitic babies. There were no abortions, miscarriages or stillbirths in the entire group. In all mothers who were treated for early (primary or secondary) syphilis seronegativity developed and remained throughout two years of observation. No information concerning the occurrence of toxic reactions is given, although the authors state that "reactions due to the treatment are appreciable" and that "penicillin will probably be as efficacious and much less hazardous."

2,3-Dimercaptopropanol (BAL) in Arsenic Poisoning.—The subject of arsenical toxicity was brought into sharp focus by the introduction of massive arsenotherapy for syphilis. In World War II, despite the increased risk of death or serious symptoms of arsenic poisoning, time-shortened schedules of metal chemotherapy were adopted by our Armed Forces for reasons of military expediency. Shortly thereafter, attention was diverted from the problem by the introduction of penicillin into clinical syphilology. However, certain disadvantages of this drug (the desirability of hospitalization and the limitations of its therapeutic effec-

118. Cormia, F. E., and Blauner, S. G.: Reactions to Twenty-Day Intensive Therapy with Mapharsen and Bismuth with a Note on the Use of BAL in Their Management. *Am. J. Syph., Gonorr. & Ven. Dis.* **31**:135 (March) 1947.

119. Curtis, A. C., and Morrow, G.: The Treatment with Massive Arsenotherapy of Early Syphilis Complicated by Pregnancy, *Am. J. Obst. & Gynec.* **52**: 284 (Aug.) 1946.

Rotman-Kavka, Hirsh and Dowling,¹³⁰ in a comparative study of penicillins X and G and crystalline penicillin G, found that penicillin X achieves and maintains higher blood concentrations than similar amounts of penicillin G. Most of the bacteria tested were more sensitive to penicillin X than to penicillin G, but the difference was slight when the two were compared on a gravimetric basis.

The relative activities of the four penicillin species, G, F, X and K, vary, depending on the micro-organism against which they are tested. Eagle¹³¹ found approximately a twofold difference in vitro between the least active and the most active of these four penicillins when tested against *Staphylococcus aureus*, group A hemolytic streptococcus and the nonpathogenic Reiter's strain of *Spirochaeta pallida*. The order of decreasing in vitro activity for these cultured spirochetes was $G > K > F = X$. The author points out that the same differences in the chemical configuration of the side group that determine the varying bactericidal activities of these penicillins may also variably affect the rate of their diffusion, excretion or inactivation in vivo and that their therapeutic activity was not necessarily parallel direct bactericidal action in vitro.

Discrepant reports concerning the effects of blood serum on the bactericidal activity of penicillin and the paradoxical finding that penicillin K is therapeutically almost inactive despite a high measure of bactericidal activity in vitro led Eagle¹³² to study the susceptibility of various crystalline penicillins to inactivation by blood. Penicillins F, G, K and X were all found to be inactivated by human and rabbit serum. Two qualitatively different mechanisms apparently were involved: one, a slow inactivation of all four penicillins by a relatively thermostable serum component; the other, a much faster inactivation observed only with penicillin K, due to a thermolabile factor in blood serum.

The urinary excretion of penicillin is so rapid that the slow destruction of penicillins F, G and X in the blood is of only secondary importance therapeutically. Nevertheless, it contributes to their rapid disappearance from the blood. The fact that penicillin X is inactivated more slowly than either F or G is reflected in blood levels which are higher and longer sustained than those afforded by the latter two species. Eagle¹³³ reports that both in man and in the rabbit penicillin

130. Rotman-Kavka, G.; Hirsch, H. L., and Dowling, H. F.: A Comparative Study of Penicillins X and G and Crystalline Penicillin G, *New England J. Med.* **236**:314 (Feb. 27) 1947.

131. Eagle, H.: The Relative Activity of Penicillins F, G, K and X Against Spirochetes and Streptococci in Vitro, *J. Bact.* **52**:81 (July) 1946.

132. Eagle, H.: The Inactivation of Penicillins F, G, K, and X by Human and Rabbit Serum, *J. Exper. Med.* **85**:141 (Feb. 1) 1947.

133. Eagle, H.: The Varying Blood Levels Afforded by Penicillin F, G, K, and X in Rabbits and Man, *J. Exper. Med.* **85**:163 (Feb. 1) 1947.

An excellent general review of the pharmacology and of the usefulness of 2,3-dimercaptopropanol in the therapy of heavy metal poisoning has been made by Brenton.¹²⁴

2,3-Dimercaptopropanol in Arsenical Poisoning from Antisyphilitic Therapy.—The results of a cooperative study of the use of 2,3-dimercaptopropanol (BAL) in the systemic treatment of arsenic poisoning have again been detailed by Eagle and Magnuson.¹²⁵ Their conclusions representing the results of therapy in 227 cases are of sufficient importance to be repeated here:

1. BAL dissolved in peanut oil with benzyl benzoate may be injected intramuscularly in man in individual doses of from 2.5 to 3 mg. per kilogram, repeated at four hour intervals. At higher dosages, an undue proportion of injections are followed by transient toxic reactions.

2. In fifty-five patients with arsenical encephalitis treated with BAL the overall mortality was 11 per cent. All fifteen patients with relatively mild cases recovered within one to four days. In severe cases, comatose or convulsing, the results varied with the time elapsed since the development of cerebral symptoms. Thus, the mortality in the first twenty-four severe patients (sic) treated with BAL from one-half to six hours after the development of symptoms was 20 per cent; while of nine patients in whom treatment was delayed for an average of thirty hours, five died. In general, the patients who recovered usually showed definite improvement in from one to two days and completely recovered in an average of four days.

3. In eighty-eight patients with arsenical dermatitis, of whom fifty-one had typical exfoliative cases, the administration of BAL usually stopped the progression of the inflammatory reaction and accelerated the healing process. The average time for definite improvement in the patients with severe cases successfully treated (80 per cent) was three days, and the average time for from 75 to 90 per cent recovery was thirteen days.

4. In ten of eleven patients with arsenical agranulocytosis the administration of BAL was followed by an increase in the total white blood cell count and an even more pronounced increase in the proportion and total number of polymorphonuclear leucocytes. The eleventh patient died.

5. In three of four patients who had in error received massive doses of arsenical (0.6, 0.4 and 0.6 Gm. mapharsen) the administration of BAL was followed by prompt symptomatic relief, and there were no late serious toxic complications. A fourth patient who received inadequate treatment with BAL after the single administration of 1.2 Gm. of mapharsen died on the seventh day.

6. In forty-four patients with a marked febrile reaction occurring as a complication of arsenotherapy, often associated with a toxic rash, the administration of BAL was usually followed by a drop in temperature and the disappearance of associated subjective symptoms. Thirty-six had completely recovered in

124. Brenton, H. L.: British Anti-Lewisite (BAL), J. Bowman Gray School Med. 5:94 (May) 1947.

125. Eagle, H., and Magnuson, H. J.: The Systemic Treatment of Two Hundred and Twenty-Seven Cases of Arsenic Poisoning (Encephalitis, Dermatitis, Blood Dyscrasias, Jaundice, Fever) with 2,3-Dimercaptopropanol (BAL), Am. J. Syph., Gonorr. & Ven. Dis. 30:420 (Sept.) 1946.

reduction in antibacterial activity was independent of any destruction of penicillin by the serum.

These data suggest that the antibacterial activity of the several penicillins is exerted only by the unbound portion of the drug and offer a possible explanation of the apparent discrepancies between the in vitro and the in vivo activity of the various penicillin species.

Tompsett, Schultz and McDermott¹³⁷ have further studied the absorption and excretion of penicillins X, G, dihydro F and K in human beings in an effort to evaluate the influence of the differences in the degrees of binding of these substances by serum protein. The duration of the serum concentrations afforded by all four penicillins after intramuscular injection of 300,000 units in human beings was uniform. Evidence is presented that previous findings of higher and more prolonged serum concentrations of penicillin X and lower, rapidly disappearing concentrations of penicillin K were artefacts created by differences in the antagonistic action of the serum on penicillin during the bioassay procedure. These differences in therapeutic effectiveness of the various penicillins could not be explained on the basis of differences in degree and duration of serum concentrations after equal doses.

Tepperman and his co-workers¹³⁸ have evidence that there is greater "inactivation" of penicillin K by the liver and kidneys than of penicillin G. It was found that penicillin levels in the blood were lower than usual in rabbits whose ureters had been ligated and still lower in animals that had been eviscerated and had had their kidneys ligated and that the lowering was greater with penicillin K than with penicillin G.

Penicillin Species in Syphilis.—With the identification and isolation of the several penicillin species, numerous attempts have been made to compare their relative effectiveness against the treponeme of syphilis. In man the ultimate comparison will require the treatment of many patients and the passage of many years. Meanwhile, the various penicillin species may be compared by any of several methods, the results of all of which are only suggestively applicable to the treatment of syphilis in man.

Olansky and Putnam¹³⁹ have tested the effectiveness of single doses of 50,000 units of two crystalline penicillins (G and X) as well as of

137. Tompsett, R.; Schultz, S., and McDermott, W.: Influence of Protein-Binding on the Interpretation of Penicillin Activity in Vivo, *Proc. Soc. Exper. Biol. & Med.* **65**:163 (June) 1947.

138. Tepperman, J.; Rakieten, N.; Valley, G., and Lyon, E. W.: Inactivation of Penicillin G and K by Liver and Kidney, *Science* **105**:18 (Jan. 3) 1947.

139. Olansky, S., and Putnam, L. E.: The Effect of the Sodium Salts of Crystalline Penicillin G, Crystalline Penicillin X, and Commercial Penicillins on Dark-field Positive Lesions of Syphilis, *J. Ven. Dis. Inform.* **27**:178 (July) 1946.

tion. They do not consider severe renal disease a contraindication to its use.

Friedham and Vogel¹²⁷ report experiments to show that the condensation product of a chemotherapeutically active arsenical with BAL may result in a new compound combining relatively low toxicity with significant spirochetocidal activity.

PENICILLIN: CHEMISTRY, PHARMACOLOGY AND EXPERIMENTAL THERAPEUTICS

The Chemistry of Penicillin.—A brief history¹²⁸ of the extensive studies in the chemistry of penicillin carried out cooperatively by English and American investigators during World War II has recently been published. As a direct result of this enormous cooperative enterprise, the synthesis of penicillin was made possible. DuVigneaud and his fellow workers at Cornell¹²⁹ report the successful synthesis of benzyl penicillin in crystalline form by the condensation of *d*-penicillamine hydrochloride and 2-benzyl-4-methoxymethylene-5 (4)-oxazolone. These workers adduce evidence, utilizing many of the newer tools of chemical science, that their synthetic preparation is truly "penicillin." The melting point, ultraviolet and infra-red absorption spectrums, refractive indexes, antibiotic activity and specific rotation of the synthetic material were similar to those of natural benzyl penicillin. Of particular significance is the fact that the synthetic material was the same optical isomer as the natural product.

While the amounts of penicillin thus far synthesized are small, the importance of this accomplishment is that new preparations chemically related to penicillin now may be produced.

Penicillin Species.—There are marked discrepancies between the in vitro and the in vivo activity of penicillins G, F, X and K. This disparity is most striking with penicillin K, which is the most active of the four in vitro but the least effective in vivo, both in bacterial and in experimental syphilitic infections. Several groups have reported that penicillin K apparently disappears from the circulating blood of man with unusual rapidity. Since the urinary excretion of penicillin K was notably low in these experiments, it was presumed that some had been destroyed within the body.

127. Friedham, E. A. H., and Vogel, H. J.: Trypanocidal and Spirochetocidal Compounds Derived from BAL and Organic Arsenicals, *Proc. Soc. Exper. Biol. & Med.* **64**:418 (April) 1947.

128. The Chemical Study of Penicillin: A Brief History, The Editorial Board of the Monograph on the Chemistry of Penicillin, *Science* **105**:653 (June 27) 1947.

129. Du Vigneaud, V.; Carpenter, F. H.; Holley, R. W.; Levermore, H. H., and Rachele, J. R.: Synthetic Penicillin, *Science* **104**:431 (Nov. 8) 1946.

8 days, the total curative dose (CD_{50}) fell from 80,000 to 1,600 to 360 units per kg., respectively. Similarly, in rabbits injected twice daily, merely doubling the number of injections from 8 to 16 and the duration of treatment from 4 days to 8 days reduced the total curative dose (CD_{50}) from 30,000 to 1,770 units per kg.

b. When the number of injections was kept constant, and only the interval between them varied, the curative dose was of the same order of magnitude whether injections were given every 4 hours, twice daily or daily (4,000, 1,770 and 4,000 units per kg.). On the other hand, when injections were given so frequently as to produce cumulative effects on the blood penicillin level, therapeutic efficacy was paradoxically reduced. Thus, the curative doses of sodium penicillin given in 16 injections at 4-hourly, 2-hourly and 1-hourly intervals were 4,000, 32,000 and more than 64,000 units per kg., respectively.

c. When the total duration of treatment was fixed, and the number of injections varied, the therapeutic efficacy of penicillin increased with the frequency of injection. In rabbits treated over a period of 4 days, as the frequency of injection was changed from once daily to twice daily to every four hours, and the number of injections correspondingly increased from 4 to 8 to 20, the total curative dose (CD_{50}) fell from 50,000 to 20,000 to 1,600 units/kg.

2. Although the therapeutic action of penicillin clearly involves both the tissue concentrations and the time over which they act, the latter time factor is by far the most important. Low concentrations acting over a long period of time (i. e., many small injections) were more effective than high concentrations acting over a short period (i. e., a few large injections to the same total dose). Within the time limits of the present experiments, the interval between injections was immaterial, provided they were not given too often: for an equal number of injections, treatment once daily was as effective as injections every 4 hours, with a suggestion of an optimum interval of 8 to 12 hours.

3. On the basis of the present experimental data, it may be anticipated that the results in the treatment of human early syphilis with sodium penicillin could significantly be improved by (a) prolonging the duration of treatment, (b) increasing the frequency and number of injections, and (c) increasing the total dosage of penicillin. The relative importance of these three factors is discussed in the text. The use of a suspension of calcium penicillin in oil and beeswax, or the administration of penicillin in a continuous intravenous, intramuscular or subcutaneous drip, or any other procedure which delays the absorption and excretion of penicillin would have the same effect as increasing the frequency and number of injections.

4. There is reason to believe that the treatment of syphilis with sodium penicillin need not be carried out in hospitalized patients, but that it may be given on an ambulatory basis once or twice daily, without necessarily sacrificing therapeutic efficacy, provided only that the patient receives the requisite total number of injections. The use of calcium penicillin in oil and beeswax, or of similar devices to delay the absorption and excretion of penicillin, may permit treatment to be given as infrequently as twice weekly, and perhaps even irregularly within that time interval.

5. The total curative dose (CD_{50}) of penicillin on the best schedule here tested was 500 units/kg. or approximately 0.3 mg./kg. of penicillin G. Milligram for milligram, penicillin is therefore 10 to 20 times as effective as mapharsen in the treatment of rabbit syphilis. In the human infection, however, penicillin is apparently only 2 to 4 times as active as mapharsen, mg. for mg.

With either penicillin or mapharsen, rabbit syphilis is easier to cure than the human disease, requiring less than $\frac{1}{4}$ to $\frac{1}{8}$ as much mapharsen, and less than $\frac{1}{20}$ to $\frac{1}{40}$ as much penicillin.

X provided higher and more sustained levels than did penicillins F and G similarly administered in equal dosage (0.6 mg. per kilogram) while penicillin K gave lower and more evanescent levels. The total amount of penicillins F, G and X recovered in the urine varied between 68 and 100 per cent, averaging 61, 87 and 74 per cent respectively in rabbits. In man, the amount of penicillins G and X recovered averaged 86 to 93 per cent respectively. In sharp contrast, the amount of penicillin K averaged 33 per cent in rabbits and 28 per cent in man. This suggests a rapid inactivation of penicillin K *in vivo*.

The therapeutic implications of these observations seem clear. By virtue of the higher and more sustained blood levels provided by penicillin X as compared with penicillins F or G, it is to be expected that the former would be more active *in vivo* than is indicated by its bactericidal activity *in vitro* relative to other penicillins. Penicillin K, on the other hand, because of its evanescent blood levels, should be far less active than its bactericidal activity *in vitro* would imply. Eagle¹³⁴ has demonstrated these facts in connection with type I pneumococci and *Streptococcus pyogenes*.

In contrast to these observations on penicillin K, Richardson and his co-workers¹³⁵ report that from a given plasma concentration the rate of disappearance of penicillin K is comparable to that of penicillin G. These investigators found in dogs that after the intravenous administration of penicillins G and K the latter was localized in the liver in higher concentrations than penicillin G. They further report that both penicillins appeared to be bound by plasma but that penicillin K was bound to a greater extent than penicillin G. Evidence is cited to suggest that the low recovery of penicillin K in plasma is not due to destruction of the penicillin and that alterations in renal excretion may be caused by its being bound by serum protein.

Tompsett, Schultz and McDermott¹³⁶ report that the antibacterial activities of penicillin species were antagonized by serum and by the albumin fraction of serum. The degrees of antagonism were quantitatively different for the several species, the extent of reduction in antibacterial activity being roughly proportional to the degree of binding of these substances as demonstrable by analysis. Moreover, the

134. Eagle, H.: The Therapeutic Activity of Penicillins F, G, K, and X in Experimental Infections with *Pneumococcus* Type I and *Streptococcus Pyogenes*, *J. Exper. Med.* **85**:175 (Feb. 1) 1947.

135. Richardson, A. P.; Miller, I.; Schumacher, C.; Jambor, W.; Pausy, F., and Lapedes, D.: Physiological Disposition of Penicillins G and K in Dogs, *Proc. Soc. Exper. Biol. & Med.* **63**:514 (Dec.) 1946.

136. Tompsett, R.; Schultz, S., and McDermott, W.: The Relation of Protein-Binding to the Pharmacology and Antibacterial Activity of Penicillins X, G, Dihydro F, and K, *J. Bact.* **53**:581 (March) 1947.

tion was of longer duration (in early syphilis the CD_{50} was 1,000 units per kilogram and in late syphilis approximately 500 units per kilogram). The occurrence of keratitis in 2 test animals whose lymph nodes had proved noninfectious causes the authors to question the validity of node transfer as a "test of cure."

Resistance to Penicillin.—From a study in which sixteen strains of bacteria were made resistant to penicillin G or penicillin X by serial passages in mediums containing increasingly larger amounts of these fractions, Dowling, Hirsh and O'Neil¹⁴⁵ conclude that "organisms which cause human infections usually do not show great differences in their relative sensitivity to penicillin G and penicillin X. In most instances, when resistance to one of these fractions increases, resistance to the other will also increase." In 2 patients with bacterial endocarditis the organisms responsible for the infection developed resistance to both penicillin fractions simultaneously.

In experiments designed to cast light on the question of whether *T. pallidum* may acquire tolerance to penicillin, Kolmer and Rule¹⁴⁶ found that in a small series of animals the Nichols-Hough strain of *T. pallidum* showed no evidence of acquired resistance to penicillin after three consecutive passages through the testes of rabbits treated with subcurative amounts of the drug.

Resistance to penicillin thus far has been no great problem in the treatment of syphilis. The possibility that penicillin-resistant strains eventually may develop, however, has not been overlooked. Nor is it unlikely that there may be developed, perhaps in the none too distant future, new antibiotic preparations therapeutically more effective against *T. pallidum* than penicillin.

A study by Sullivan, Stahly and Birkland¹⁴⁷ is of interest in this connection. These investigators studied reciprocal sensitivities to penicillin, streptomycin and streptothricin of strains of *Staph. aureus* which had been made resistant *in vitro* to each of these three antibiotic substances. The development of maximal resistance was accomplished after twelve transfers for streptomycin, twenty-five transfers for streptothricin and thirty-two transfers for penicillin. The principal purpose was to determine whether the development of resistance to one of the

145. Dowling, H. G.; Hirsh, H. L., and O'Neil, C. B.: Studies on Bacteria Developing Resistance to Penicillin Fractions X and G *In Vitro* and in Patients Under Treatment for Bacterial Endocarditis, *J. Clin. Investigation* **25**:655 (Sept.) 1946.

146. Kolmer, J. A., and Rule, A. M.: Acquired Resistance of *Treponema Pallidum* to Penicillin, *Proc. Soc. Exper. Biol. & Med.* **63**:240 (Nov.) 1946.

147. Sullivan, M.; Stahly, G. L., and Birkland, J. M.: Reciprocal Sensitivities of *Staphylococcus Aureus* to Streptomycin, Streptothricin and Penicillin, *Science* **104**:397 (Oct. 25) 1946.

several commercial varieties on the rate of disappearance of spirochetes in dark-field-positive lesions of early syphilis. All types of penicillin tested had some spirocheticidal activity as demonstrated by the accelerated disappearance of surface treponemes. Crystalline penicillin G appeared at least as effective as any of several commercial penicillin preparations and penicillin X somewhat less effective than penicillin G.

Tucker and Robinson¹⁴⁰ have sought to determine a quantitative relationship between dosage (of penicillin G) and the disappearance time of surface *Treponema pallida*. These authors report the results of serial dark field studies of 35 patients with early syphilis. The sodium salt of penicillin G was administered on a gravimetric basis, and dark field examinations were performed at intervals of forty-eight hours. An inverse relationship between the dosage of penicillin G and the time required for disappearance of surface treponemes was demonstrated. Variability among patients receiving comparable dosages was, however, great enough to make the method unsatisfactory for the assay of penicillin preparations in man.

Methods of Administration.—Seeking information on the optimum time-dose relationships in the administration of sodium penicillin in the treatment of syphilis, Eagle, Magnuson and Fleischman¹⁴¹ note that at least three variables may modify therapeutic efficacy, i. e., the number of injections, their frequency and the total amount of penicillin administered. The multiple permutations of these three variables have been studied in experimental syphilis in rabbits. The curative dose of penicillin sodium for syphilis in rabbits was found to be influenced to a striking degree by the number of injections. The greater the number, the less was the total amount of penicillin required for cure. On the other hand, provided the interval between injections was sufficiently long to avoid cumulative effects on the blood penicillin level (in which case therapeutic efficacy was paradoxically decreased) there appeared to be little difference whether penicillin was administered every four hours, twice daily or daily; an equal number of injections at a given dosage level produced comparable effects.

This extensive study is summarized by the authors as follows:

1. The therapeutic efficacy of sodium penicillin in experimental syphilis is profoundly modified by the method of its administration.

- a. In rabbits injected at 4-hour intervals, as the number of injections was increased from 8 to 20 to 50, and the duration of treatment from 32 hours to

140. Tucker, H. A., and Robinson, R. C. V.: Disappearance Time of *Treponema Pallidum* from Lesions of Early Syphilis Following Administration of Crystalline Penicillin G, *Bull. Johns Hopkins Hosp.* **80**:169 (March) 1947.

141. Eagle, H.; Magnuson, H. J., and Fleischman, R.: The Effect of the Method of Administration on the Therapeutic Efficacy of Sodium Penicillin in Experimental Syphilis, *Bull. Johns Hopkins Hosp.* **79**:168 (Aug.) 1946.

blood levels for twenty-four hours has been made by Cannon, Lindstrom and Ospeck.¹⁵¹ These authors' experiments with various oily diluents for penicillin indicate that of the oils tested peanut oil with a 4.8 per cent mixture of beeswax and hydrogenated cottonseed oil (melting point, 40 C.) produced the most satisfactory prolongation of the penicillin action. Increase of the dosage of penicillin at each injection not only heightened the level of penicillin in the blood but also prolonged (slightly) the duration of its action.

Incorporation of penicillin in vehicles of the water in oil type was found by Harris, Wilcox and Finland¹⁵² to give only a slight and inconstant prolongation of penicillin levels in the blood.

There are technical difficulties in the administration of penicillin in a suspension of oil and 4.8 per cent beeswax. The preparation originally devised by Romansky and Rittman is in a solid state at room temperature and must be heated before injection is possible. A new preparation of unstated composition¹⁵³ that is fluid at room temperature is reported by Hirsh and his co-workers¹⁵⁴ to give prolonged penicillin levels in the blood, which, however, are somewhat inferior to those obtained with the original "Romansky formula."

Clinical Use of Penicillin-Oil-Beeswax.—Data from a study of 600 cases and from the clinical observation of 4,000 patients given 60,000 injections of penicillin calcium in beeswax and peanut oil are given in detail by Romansky.¹⁵⁵ The results in a variety of infections were "as satisfactory as those obtained by the multiple injections of penicillin in aqueous solution." The incidence of allergic reactions (urticaria and angioneurotic edema) after intramuscular injections of penicillin-oil-beeswax was approximately 5 per cent. Local reactions at the site of injection occurred, but they were more frequent when the preparation was given subcutaneously. The author was able to demonstrate that penicillin calcium in beeswax and peanut oil showed no loss of potency at room temperature for at least one year. At 37 C. potency was maintained for about nine months.

151. Cannon, A. B.; Lindstrom, K., and Ospeck, A. G.: Maintenance of Penicillin Blood Levels After a Single Intramuscular Injection of Penicillin in Various Oils, *Science* **104**:414 (Nov. 1) 1946.

152. Harris, H. W.; Wilcox, C., and Finland, M.: Plasma Levels After Repository Injections of Penicillin in Water-in-Oil Emulsions, *Proc. Soc. Exper. Biol. & Med.* **63**:199 (Oct.) 1946.

153. Obtained from Merck & Co., Inc., Rahway, N. J.

154. Hirsh, H. L.; Dowling, H. F.; Vivino, J. J., and Rotman-Kavka, G.: Penicillin in Beeswax and Peanut Oil: A New Preparation Which Is Fluid at Room Temperature; Absorption and Therapeutic Use, *J. Lab. & Clin. Med.* **32**: 34 (Jan.) 1947.

155. Romansky, M. J.: The Current Status of Calcium Penicillin in Beeswax and Peanut Oil, *Am. J. Med.* **1**:395 (Oct.) 1946.

Eagle and his associates have also shown (to be referred to in the section on the prophylaxis of syphilis) that the curative dose of penicillin in rabbit syphilis is directly related to the size of the inoculum and the duration of infection.

Hoffman¹⁴² has made a comparison between the intramuscular and subcutaneous methods of administering aqueous solutions of penicillin. Three purified preparations were used and plasma levels of penicillin determined at half an hour, two and one-half hours and three hours after a single injection. Three dosage levels were employed. There were no significant differences between the plasma levels of penicillin obtained after subcutaneous injection and those obtained after intramuscular administration. All three purified preparations, the amorphous and crystalline penicillin sodium and crystalline penicillin potassium, gave essentially the same results. With purified penicillin, there were practically no local reactions of the "bee sting" type, which are not uncommon with more impure preparations.

Experimental Therapeutics.—The experiments of Arnold, Mahoney and Cutler¹⁴³ indicate that rabbits with early syphilis that have been treated with amounts of penicillin sufficient to effect biologic "cure" (as adjudged by lymph node transfers four months after treatment) can be reinfected with a homologous strain within ten days after treatment is completed. These experiments are important in that they imply that "cure" may be effected during the actual period of treatment, since reinfection is successful while the healing chancre of the first infection is still present and (although these authors did not study the point) while reagin produced by the first infection is still present in the blood.

Fleming and Wolf¹⁴⁴ have assayed the therapeutic effectiveness of relatively crude commercial penicillin in early (six weeks' duration) and late (six months' duration) syphilis in rabbits. Their method of treatment, intramuscular injections of an aqueous solution every three hours for thirty-two injections, was the same for rabbits with early as for those with late syphilis. The total amount of penicillin required to "cure" 50 per cent of the test animals (as adjudged by negative lymph node transfers eight weeks after treatment, the inadequacy of which the authors themselves recognize) was lower in the group whose infec-

142. Hoffman, W. S.: Subcutaneous Versus Intramuscular Administration of Penicillin, *J. Lab. & Clin. Med.* **31**:1165 (Nov.) 1946.

143. Arnold, R. C.; Mahoney, J. F., and Cutler, J. C.: Reinfection in Experimental Syphilis in Rabbits Following Penicillin Therapy, *Am. J. Syph., Gonorr. & Ven. Dis.* **31**:264 (May) 1947.

144. Fleming, W. L., and Wolf, M. H.: The Therapeutic Effectiveness of Relatively Crude Commercial Penicillin in Early and Late Rabbit Syphilis, *Am. J. Syph., Gonorr. & Ven. Dis.* **30**:468 (Sept.) 1946.

daily over a period of eight days, it was 16,000 units. The minimal curative dose of penicillin-oil-beeswax by intramuscular injection once a day for eight days was approximately 8,000 units; given twice daily, it was, paradoxically, 16,000 units.

Inhibitory Effect of Caronamide on Renal Excretion of Penicillin.— Attempts have been made to decrease the renal excretion of penicillin by the administration of iodopyracet injection ("diodrast") and paraaminohippuric acid, but both of these substances must be given in large amounts by continuous intravenous infusion. A new approach to the problem of decreasing the urinary excretion of penicillin involves the use of a compound, 4'-carboxyphenylmethanesulfonanilide, called by Beyer¹⁵⁸ caronamide. Unlike "diodrast" and paraaminohippuric acid, which compete with penicillin on a mass action basis for transport through the renal tubules, caronamide does not appear to be excreted by the tubules but is believed to suppress penicillin excretion by blocking an enzyme system involved in the transport of penicillin through the tubular cells. The compound is rapidly absorbed from the gastroenteric tract and therefore may be given orally.

The oral administration of caronamide was found by Vermey and Miller¹⁵⁹ to enhance the therapeutic effectiveness of intramuscularly administered penicillin in mice experimentally infected with type I pneumococci or *Eberthella typhosa*. Since caronamide has no demonstrable bactericidal action of its own and does not enhance that of penicillin in vitro, it is believed that the increased effectiveness of penicillin results from the influence of caronamide on the duration and magnitude of blood and tissue levels of penicillin.

PENICILLIN IN THE TREATMENT OF SYPHILIS

Like many another new form of therapy, penicillin therapy of syphilis is progressing through the cycle of enthusiasm and reaction. The limitations of this form of therapy gradually are becoming apparent. Even the most skeptical observer no longer denies that penicillin is a valuable adjunct to syphilotherapy or that it is in some respects superior to any previous form of treatment. That it has serious drawbacks is recognized by its most ardent protagonists.

Until recently, the literature on the use of penicillin in syphilis has been confined almost exclusively to American and British journals. Within the past year, general discussions of the subject have become

158. Beyer, K. H.: New Concept of Competitive Inhibition of the Renal Tubular Excretion of Penicillin, *Science* **105**:94 (Jan. 24) 1947.

159. Vermey, W. F., and Miller, A. K.: Effect of Caronamide upon Penicillin Therapy of Experimental Pneumococcus and Typhoid Infections in Mice, *Proc. Soc. Exper. Biol. & Med.* **65**:222 (June) 1947.

antibiotic agents would result in resistance to one or both of the others. It was found that the strains which were resistant to streptothricin also were more resistant to streptomycin than were those in the parent culture but that the reverse of this was not true. With this one exception the development of resistance to one antibiotic agent did not result in increased resistance to either of the others.

Effect of Hyperpyrexia on Activity of Penicillin.—Having previously demonstrated¹⁴⁸ that the rate at which cultured spirochetes (Reiter) are killed in vitro increases with elevations in temperature, Eagle and his co-workers¹⁴⁹ have confirmed this observation in vivo against pathogenic strains of *T. pallidum*. When penicillin was injected intramuscularly in syphilitic rabbits every two hours for sixteen injections, it required 30,000 to 60,000 units per kilogram to cure 50 per cent and 90 per cent of the rabbits respectively. When the body temperature of rabbits during the period of administration of penicillin was increased by approximately 3 to 4 degrees over an average ten hour period, the total curative dose for 50 per cent of the animals fell to 3,000 and 8,000 units per kilogram. The authors consider that the favorable effect of fever on the therapeutic activity of penicillin in early syphilis at least in part reflects an enhanced spirocheticidal action of penicillin at higher temperatures, but they point out that fever may have a spirocheticidal effect of its own additive or synergistic to that of penicillin.

PROLONGATION OF ACTION OF PENICILLIN

One of the major disadvantages of penicillin as a therapeutic agent is the rapidity with which it is excreted in the urine. Relatively large doses must be given every few hours if detectable plasma concentrations are to be maintained. Many attempts have been made to prolong the therapeutic activity of penicillin. These attempts have in general been calculated either to delay the absorption of the drug or to decrease its renal excretion.

Delayed Absorption of Penicillin.—By far the most satisfactory method of delaying absorption after parenteral injection is the administration of penicillin in peanut oil and beeswax (Romansky and Rittman¹⁵⁰).

A preliminary report of studies to determine the most satisfactory diluent for penicillin from the standpoint of maintaining satisfactory

148. Eagle, H., and Musselman, A. D.: The Spirocheticidal Action of Penicillin in Vitro and Its Temperature Coefficient, *J. Exper. Med.* **80**:493, 1944.

149. Eagle, H.; Magnuson, H. J., and Fleischman, R.: The Effect of Hyperpyrexia on the Therapeutic Efficacy of Penicillin in Experimental Syphilis, *Am. J. Syph., Gonorr. & Ven. Dis.* **31**:239 (May) 1947.

150. Romansky, M. J., and Rittman, G. E.: Penicillin Blood Levels for Twenty-Four Hours Following a Single Intramuscular Injection of Calcium Penicillin in Beeswax and Peanut Oil, *New England J. Med.* **233**:577 (Nov. 15) 1945.

daily dose for an adult should be 2 cc. (600,000 units) and a total duration of treatment from 8-15 days or longer, depending on the stage of the infection. For early syphilis, a minimum total dose of 4.8 to 6.0 million units of this preparation is advised.

Calcium penicillin in peanut oil-beeswax should not be administered by the subcutaneous route, since under these circumstances the incidence of sensitizing reactions, with giant urticaria and angioneurotic edema, is excessively high.

3. There is evidence, both from the experimental laboratory and the clinic, that the addition of arsenic (mapharsen or its analogues) in subcurative dosage to a penicillin treatment schedule enhances the therapeutic effect of each drug. A suggested total dose of an arsenoxide for this purpose is 300-600 mgm., administered in divided intravenous injections of 40-60 mgm. each, over a total time period of 1-4 weeks.

It is recognized that the administration of arsenic in this dosage introduces a risk of serious reactions or death, in inverse proportion to the time interval of its administration. If 300-360 mgm. are given within 7-9 days, the expected mortality rate is approximately 1:3,000 to 1:4,000. If the same dosage is given over a total period of four weeks, this risk is reduced to about 1:30,000.

In view of this consideration, and of possible technical difficulties encountered in the administration of arsenic or in the mere prolongation of treatment necessitated thereby, opinion is divided as to the desirability of including this drug in a recommended penicillin treatment schedule. The majority opinion of a group of competent experts is that the results of penicillin alone, in the dosage and time recommended above, would be satisfactory in a sufficiently large proportion of patients with early syphilis treated for the first time to justify eliminating arsenic from the original course of treatment, reserving its use for relapsing cases.

4. There is both clinical and experimental evidence to indicate that an insoluble bismuth salt administered intramuscularly in an oil suspension, e.g., bismuth subsalicylate, produces a slowly absorbed bismuth depot which continually releases small amounts of therapeutically effective bismuth for a period of from 3 to 6 months. There is likewise evidence to indicate that bismuth added to arsenic materially improves the results of metal chemotherapy. If bismuth is added to a penicillin or penicillin-arsenic schedule for early syphilis, it may be anticipated that the incidence of infectious relapse within the first 6 to 12 months after treatment will be materially reduced. This is probably accomplished, for the first few months after treatment, by bismuth effect alone. Later relapse is perhaps prevented or minimized by the fact of development of the patient's own immunity. Whether or not bismuth is of value in effecting cure of the individual patient, it should nevertheless be of considerable aid in minimizing infectious relapse, and thereby reducing the risk of spread of infection.

If bismuth is employed, the individual dose should be 200 mgm. (0.2 gm.) (*expressed as the subsalicylate, not as bismuth metal*). A total of 1,000 mgm. (5 injections) given every other day for a total of 9 days is unlikely to produce stomatitis except in patients with extremely bad oral hygiene, or renal damage in patients with previously undamaged kidneys. If the total dose is larger than 1,000 mgm., injections should be given not oftener than twice weekly.

However, the opinion of a group of experts is also divided as to the desirability of including bismuth with the original course of penicillin in early syphilis. The majority believed, as for arsenic, that bismuth should be reserved for use in relapsing cases.

It should be emphasized that these suggestions for the use of penicillin in early syphilis represent a combination of medical desirability and expediency.

Penicillin-Oil-Beeswax in Experimental Syphilis.—The experiments of Eagle, Magnuson and Fleischman¹⁵⁶ establish the fact that in experimental syphilis in rabbits a single injection of penicillin in oil and beeswax is more effective therapeutically than a single injection of the aqueous solution and at least as effective as multiple small injections.

When an attempt was made to cure rabbits with early syphilis by a single massive injection, more than 600,000 units of an aqueous solution of penicillin per kilogram was required to cure one half of the animals, while with penicillin-oil-beeswax the CD_{50} was only 50,000 units per kilogram. As the total number of injections was increased, the relative advantage of the oil-beeswax preparation progressively diminished. To cure early rabbit syphilis in one day with a total of 50,000 units required one injection of the oil-beeswax preparation and twelve injections of the aqueous solution, to effect cure in four days with a total of 3,500 units per kilogram required four injections of oil-beeswax and sixteen of the aqueous solution and to cure in eight days with 800 units per kilogram required sixteen injections of the oil-beeswax preparation and thirty-two of the aqueous solution. Thus penicillin in aqueous solution had to be subdivided into two to fourteen times as many injections as the oil-beeswax suspension in order to be equally effective.

These experiments indicate a consistent superiority of penicillin in oil and beeswax over penicillin in aqueous solution. Unfortunately they were not carried out to their logical conclusion. With further subdivision of the doses of penicillin in aqueous solution it is entirely possible that the superiority of penicillin-oil-beeswax would be equaled and perhaps surpassed in therapeutic effectiveness by the aqueous solution.

Kolmer¹⁵⁷ has studied the therapeutic efficacy of penicillin in experimental early syphilis in rabbits and has compared its activity in isotonic solution of sodium chloride with that in suspension in peanut oil and beeswax. His results, unimpressive because of the small number of test animals used, suggest a unit for unit superiority of the peanut oil-beeswax suspension. In isotonic solution of sodium chloride the minimal single curative dose of penicillin by intramuscular injection was more than 100,000 units per kilogram of weight, whereas in oil-beeswax suspension it was approximately 40,000 units. Given twice

156. Eagle, H.; Magnuson, H. J., and Fleischman, R.: Observations on the Therapeutic Efficacy in Experimental Syphilis of Calcium Penicillin in Oil and Beeswax and Their Bearing on Its Use in Man, *Am. J. Syph., Gonorr. & Ven. Dis.* **31**:247 (May) 1947.

157. Kolmer, J. A.: Penicillin in the Treatment of Experimental Syphilis of Rabbits: I. The Therapeutic Activity of Penicillin in Single and Multiple Doses in Isotonic Solution of Sodium Chloride and Peanut Oil-Beeswax by Intramuscular Injection, *Arch. Dermat. & Syph.* **55**:741 (June) 1947.

TABLE 2.—Results Twelve to Fifteen Months After Treatment for Secondary Syphilis in Rapid Treatment Centers

Schedule of Therapy	Total Patients Observed for 12 to 15 Months	Cumulative Per- centage Retreated	Patients with Clinically Negative Reactions			
			Seropositive		Seronegative	
			No.	%	No.	%
Penicillin only						
600,000 units, 10,000 every 3 hr.....	197	32.9	25	12.7	107	54.3
1,200,000 units, 20,000 every 3 hr.....	131	26.5	14	10.7	82	62.8
1,200,000 units, 40,000 every 3 hr.....	247	21.0	42	17.0	153	62.0
1,200,000 units, 40,000 every 6 hr.....	319	22.7	63	19.8	183	57.4
1,500,000 units, 20,000 every 2 hr.....	28	22.4	5	17.6	17	59.9
1,600,000 units, 20,000 every 3 hr.....	189	20.8	47	24.9	102	54.1
1,700,000 units, 20,000 every 2 hr.....	45	21.3	9	20.2	26	58.4
2,400,000 units, 40,000 every 3 hr.....	247	21.0	42	17.0	153	62.0
2,400,000 units, 80,000 every 3 hr.....	171	21.1	29	16.9	106	61.9
Penicillin (peanut oil and beeswax)						
4,800,000 units, 300,000 every 12 hr.....	38	13.1	6	15.8	27	71.0
4,800,000 units, 600,000 every 24 hr.....	39	18.2	7	15.1	31	66.8
Penicillin and oxophenarsine hydrochloride						
300,000 units, 5,000 every 3 hr.; 320 mg. of oxophenarsine hydrochloride, 40 mg. each day "8-3-0".....	41	29.6	8	19.4	21	51.0
1,200,000 units, 20,000 every 3 hr.; 320 mg. of oxophenarsine hydrochloride 40 mg. each day "8-12-0".....	415	16.6	65	15.7	281	67.7
1,200,000 units, 16,667 every 3 hr.; 1 mg. per kilogram (maximum, 60 mg. of oxophenarsine hydrochloride on 1st, 3d, 5th, 7th and 9th days) "5-12-0"....	221	16.9	56	25.3	128	57.8
Penicillin, oxophenarsine hydrochloride and bismuth						
600,000 units, 10,000 every 3 hr.; 1 mg. per kilogram (maximum, 60 mg. of oxophenarsine hydrochloride on each of 8 days); 200 mg. of bismuth on 1st, 5th and 8th day "8-6-3".....	787	18.4	210	26.7	432	56.9
1,200,000 units, 16,667 every 3 hr.; 1 mg. per kilogram (maximum, 60 mg. of oxophenarsine hydrochloride on 1st, 3d, 5th, 7th and 9th day); 200 mg. of bismuth on 1st, 5th and 9th day "5-12-3"	632	15.1	201	31.8	336	53.1
Penicillin and fever therapy						
600,000 units in 42 hours; 8 to 10 hours of fever sustained at 104 to 106 F....	47	44.1	6	12.9	20	42.9
1,200,000 units in 29½ hours; 6 hours of fever sustained at 106 F.....	80	26.1	9	11.3	50	62.6
1,200,000 units, 20,000 every 3 hr.; 3 ses- sions of fever of 3 hours each.....	36	14.2	1	2.8	30	83.2
One day fever therapy — temperature maintained at 105 to 106 F. for 6 to 8 hours; 150 mg. of bismuth; 1.7 or more mg. per kilogram of oxophen- arsine hydrochloride (or total of 120 mg.)						
349	23.2	37	10.6	231	66.3	
Five day intravenous drip—1,200 mg. of oxophenarsine hydrochloride.....						
130	11.1	25	19.2	91	69.7	
Eight day intravenous drip—1,080 to 1,200 mg. of oxophenarsine hydrochloride and 12 injections of bismuth.....						
231	11.1	50	21.7	155	67.2	
Schoch (11 to 20 days)—1,200 or more mg. of oxophenarsine hydrochloride and varying amounts of bismuth.....						
105	15.4	29	27.6	60	57.0	

available in French,¹⁶⁰ Spanish,¹⁶¹ Dutch¹⁶² and German¹⁶³ publications. Recent American summations include those of O'Leary and Kierland¹⁶⁴ and Reynolds.¹⁶⁵

Penicillin in Early Syphilis.—Moore⁵ in his monograph on penicillin in syphilis makes the following suggestions for the use of commercial penicillin in early syphilis:

1. When sodium penicillin in aqueous solution is used for the treatment of syphilis in man, injections should be given by the intramuscular route every 2-4 hours, preferably every 2-3 hours day and night around the clock, for a minimum of 7½-8 days.

The minimum dose of previously produced and presently available commercial penicillin should be, for *seronegative primary syphilis*, not less than 3.6 million units (90 injections of 40,000 units each, given every 2 hours; or 60 injections of 60,000 units each, given every 3 hours); for *seropositive primary and early secondary syphilis*, not less than 5.4 million units (90 injections of 60,000 units each or 60 injections of 90,000 units each).

For a first relapse (including reinfection, infectious or serologic relapse) of early syphilis after previous treatment of early syphilis, the above course should be repeated; *plus* 360 mgm. mapharsen (or an analogue) given twice to three times weekly in 6 individual intravenous injections of 60 mgm. each; *plus* 1,200 mgm. bismuth subsalicylate, given twice weekly in 6 individual intramuscular injections of 0.2 gm. each.

For a second relapse of early syphilis after previous penicillin treatment, the patient should be transferred from penicillin entirely and placed on metal chemotherapy with arsenic and bismuth, preferably by the 26 week schedule employed by the Army and Navy (40 intravenous injections of mapharsen, or an analogue, 16 intramuscular injections of bismuth subsalicylate).

2. The only presently satisfactory method of absorption delaying of penicillin is the administration of calcium penicillin in peanut oil-beeswax. Detailed information is not yet available as to the effects of this preparation in large series of patients with early syphilis, or with any other stage of the disease. It is known, however, that a single intramuscular injection of 600,000 units will produce a therapeutically active blood level for from 20-28 hours. If calcium penicillin in peanut oil-beeswax is used in any stage of syphilitic infection, the average

160. Bouvier, J. B.: La pénicilline dans la traitement de la syphilis, Paris méd. 36:554 (Dec. 14) 1946. Pautrier, L. M.: Quelle place la pénicilline peut-elle prendre à l'heure actuelle dans le traitement de la syphilis, Presse méd. 55:187 (March 19) 1947.

161. Spilzinger, C.; Gunche, F. F., and Bigatti, A.: Penicilina y sífilis, Rev. Asoc. méd. argent. 61:3 (Jan.-Feb.) 1947. Reynolds, F. W., and Pardo, O. A.: La penicilina en el tratamiento de sífilis precoz, Am. clínica 10:314 (April) 1947.

162. de Bergh, J.: Over de behandeling van syphilis met penicilline, Nederl. tijdschr. v. geneesk. 90:1672 (Nov. 16) 1946.

163. Bohnstedt, R. M.: Behandlung der Syphilis mit Penicillin, Ztschr. f. Haut- u. Geschlechtskr. 12:396 (June) 1947.

164. O'Leary, P. A., and Kierland, R. R.: Today's Treatment of Syphilis, J. A. M. A. 132:430 (Oct. 26) 1946.

165. Reynolds, F. W.: Penicillin in the Treatment of Syphilis, Am. J. Med. 1:661 (Dec.) 1946.

syphilis, in 89.9 per cent of 564 cases of seropositive primary syphilis and in 83.0 per cent of 236 cases of secondary syphilis. The cerebrospinal fluid of 719 patients was examined after therapy. It was normal in 714 and abnormal in 5 (0.69 per cent). The high over-all satisfactory progress rate (90.6 per cent), admittedly tentative because of inadequate follow-up, was attributed to the considerable proportion of cases in which the disease was in the primary stage (83.1 per cent) and to the fact that the patients probably received penicillin of satisfactory potency. There were 40 for whom the treatment failed (5 per cent) among the 790 white patients, as contrasted with 92 (15 per cent) among the 610 Negro patients. The implications of the disparity with respect to race are thought possibly to involve a higher incidence of reinfection among the Negro troops. Reinfection might be expected to occur more frequently in the Negro groups since the incidence of

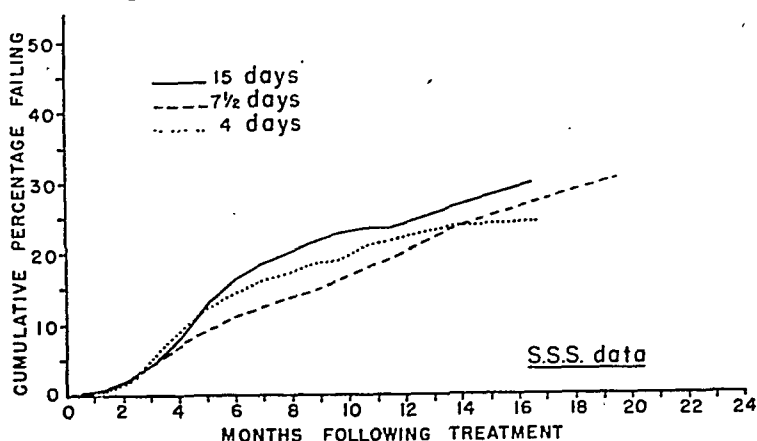


Fig. 3.—Cumulative failure rates by duration of therapy—penicillin alone, 2,400,000 units in injections given every three hours.

syphilis among them was consistently twelve to fifteen times that among the white troops.

5. Aqueous solution of penicillin versus penicillin-oil-beeswax. The therapeutic results with penicillin in oil and beeswax are at least as good as those with any schedule involving aqueous solutions of penicillin.

Favorable results in small series of patients treated with penicillin in oil and beeswax have been reported by Koch¹⁷² and by Romansky and Rein.¹⁷³ Thomas, Landy and Cooper¹⁷⁴ have treated, with "unusually satisfactory" results, 802 patients with primary or secondary syphilis

172. Koch, R. A.: Ambulatory Intensive Treatment of Syphilis with Calcium Penicillin, in Oil and Wax, *Urol. & Cutan. Rev.* **50**:461 (Aug.) 1946

173. Romansky, M. J., and Rein, C. R.: Treatment of Early Syphilis with Calcium Penicillin-Oil-Beeswax, *J. A. M. A.* **132**:847 (Dec. 7) 1946.

174. Thomas, E. W.; Landy, S., and Cooper, C.: Rapid Treatment of Early Syphilis with Penicillin in Beeswax and Oil, *J. Ven. Dis. Inform.* **28**:19 (Feb.) 1947.

They are based on presently available information, are tentative only, and are subject to revision within the next few months as further information accumulates.

It is also most vigorously to be emphasized that in the adoption of penicillin therapy for syphilis, the eventual value of which will not be determined for several years to come, the physician has a particular responsibility for careful follow-up and frequently repeated post-treatment observation on all patients so treated.

There have been in progress in the United States two extensive studies of various penicillin schedules for the rapid treatment of early syphilis. The results obtained by the thirty-six clinics¹⁶⁶ cooperating with the Syphilis Study Section of the National Institute of Health have recently been summarized by Merrell.¹⁶⁷ Those reported by the Cooperating Rapid Treatment Facilities¹⁶⁸ of the United States Public Health Service have been published by Heller.¹⁶⁹ The most recent compilation is outlined in a progress report dated December 1946.¹⁷⁰ The results obtained by the Syphilis Study Section are expressed in terms of cumulative failure rates and those obtained by the rapid treatment centers in terms of cumulative retreatment rates (table 2).

From the extensive data of the Syphilis Study Section and the rapid treatment centers there are now emerging several facts regarding the use of penicillin in early syphilis:

1. Dosage. Total doses of penicillin amounting to 1,200,000, 2,400,000 and 4,800,000 units are of about the same therapeutic effectiveness (fig. 1). With smaller total doses (300,000 and 600,000 units) there is an even greater percentage of treatment failures.

2. Interval between injections. There are no apparent differences between schedules of therapy in which the injections of aqueous solution of penicillin are given every two hours, every three hours or every six hours (fig. 2).

3. Duration of treatment. When other variables in the treatment schedule are held constant and only the duration of treatment varied,

166. Several of the clinics (Bauer and others: *Am. J. Syph., Gonor. & Ven. Dis.* **31**:45 [Jan.] 1947; Bundesen and others: *ibid.* **30**:475 [Sept.] 1946; Smith and others: *Arch. Dermat. & Syph.* **55**:644 [May] 1947) have reported their results separately and in detail. Since all the material is incorporated in the data of the Central Statistical Unit, these articles are not reviewed.

167. Merrell, M.: Results of the Nation-Wide Study of Early Syphilis (available in mimeographed form).

168. At least two rapid treatment centers (Leavitt, H. M.: *Am. J. Syph., Gonor. & Ven. Dis.* **31**:27 [Jan.] 1947; Holley, H. L.: *ibid.* **31**:41 [Jan.] 1947) have reported their data separately.

169. Heller, J. R., Jr.: Results of Rapid Treatment of Early Syphilis, *J. Ven. Dis. Inform.* **27**:217 (Sept.) 1946; Results of Rapid Treatment of Early Syphilis, *J. A. M. A.* **132**:258 (Oct. 5) 1946.

170. Rapid Treatment of Early Syphilis: Progress Report, Cooperating Rapid Treatment Facilities and U. S. Public Health Service, Venereal Disease Division, December 1946.

despite Eagle, Magnuson and Fleischman's report ¹⁷⁶ that in experimental rabbit syphilis there is a significant increase in the therapeutic efficacy of penicillin at fever temperatures.

7. Types of failure. In the data of the Syphilis Study Section the treatment failures are separated into three groups according to the ascribed cause of failure: (1) clinical relapse; (2) serologic relapse or seroresistance, and (3) probable reinfections (a "consensus of opinion" classification that lacks objectivity).

There were no great differences among the various schedules of treatment with respect to the incidence of clinical relapses, which at seventeen months varied from about 3 to 7 per cent. The distribution of treatment failures was, in general, approximately that shown in figure 5.

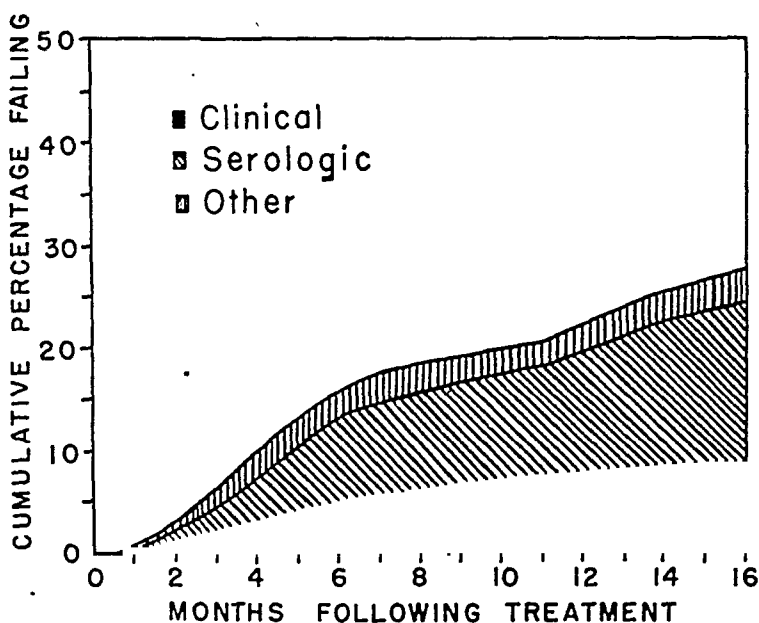


Fig. 5.—Cumulative failure rates by types of failure—penicillin alone, 1,200,000 units.

8. Reactions to rapid therapy. Throughout all the reports, the relative safety of schedules using penicillin alone as compared with schedules combining oxophenarsine hydrochloride with penicillin is apparent. In the experiences of the cooperating rapid treatment centers, there were no fatalities when penicillin was used without other drugs. The rate of severe reactions per thousand patients treated was only 8.6 for penicillin sodium alone and 5.1 for penicillin-oil-beeswax (table 3.)

A total of 11 deaths from treatment occurred when oxophenarsine hydrochloride was used concurrently with penicillin: the rate was 1 death for every 5,700 patients treated with this drug in combination

176. Eagle, H.; Magnuson, H. J., and Fleischman, R.: The Effect of Hyperpyrexia in the Therapeutic Efficacy of Penicillin in Experimental Syphilis, *Am. J. Syph., Gonorr. & Ven. Dis.* **31**:239 (May) 1947.

it appears to make little difference whether penicillin is given over a period of four days, seven and a half days or fifteen days (fig. 3).

4. Stage of the disease. From all available reports it is apparent that the results of penicillin therapy are significantly more satisfactory when treatment is started early in the course of the disease. Nowhere is this more strikingly illustrated than in the results of penicillin therapy in the Army.

Sternberg and Leifer¹⁷¹ have analyzed the Army records of 1,400 soldiers with early syphilis treated with 2,400,000 units of penicillin in

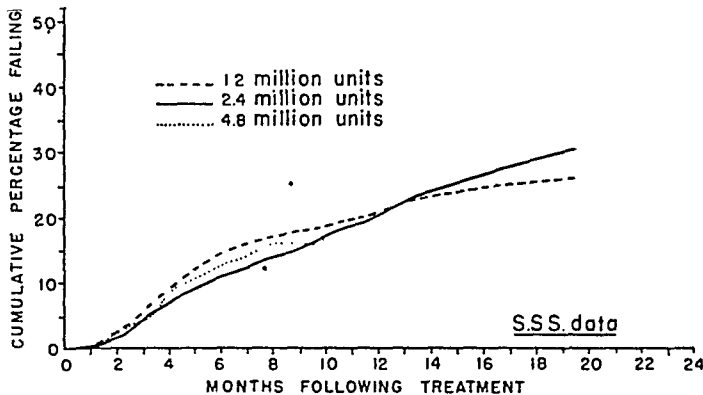


Fig. 1.—Cumulative failure rates by total dosage of penicillin—penicillin alone, administered in divided doses every three hours for seven and one-half days.

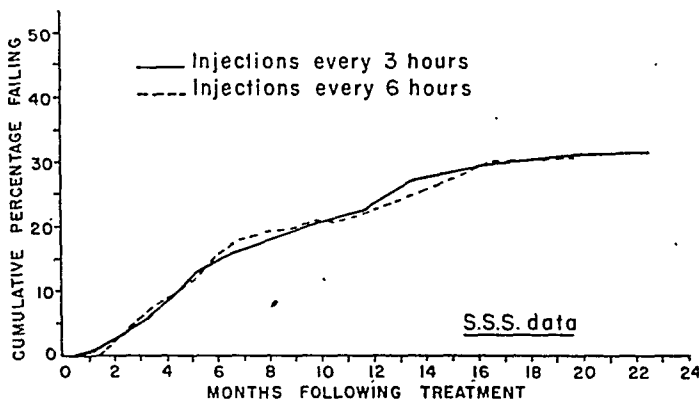


Fig. 2.—Cumulative failure rates by time interval between injections of penicillin—penicillin alone, 1,200,000 units over a period of four days.

aqueous solution given in divided doses over a period of seven and one-half days. There were no severe toxic reactions, and all patients completed the prescribed course of treatment. Satisfactory progress was observed in 94.3 per cent of 600 cases of seronegative primary

171. Sternberg, T. H., and Leifer, W.: Treatment of Early Syphilis with Penicillin, *J. A. M. A.* **133**:1 (Jan. 4) 1947.

syphilis and one free from the undesirable reactions of arsenotherapy. They believe that this form of therapy combines the treponemicidal action of penicillin with a desirable prolonged suppressive effect from bismuth.

Hazel¹⁸² has employed a treatment schedule in a small series of patients with early syphilis of ten daily injections of penicillin-oil-beeswax administered concomitantly with oxophenarsine hydrochloride every other day. After the completion of this intensive treatment the administration of the arsenical was continued once weekly until a total of twenty injections had been given; treatment was then concluded with five weekly injections of bismuth subtartrate. Schedules of this type are adaptable to office practice. Judging from this author's early experience, they would appear to be highly efficacious.

The Serologic Response Following Penicillin Therapy.—Data comparing the serologic response following penicillin therapy with that following previously established methods of treatment have been presented by Clark, Maxwell and Scott.¹⁸³ The effects of age, sex, race, duration of infection and asymptomatic neurosyphilis on serologic responses are considered. The serologic changes observed during the first eight weeks after penicillin therapy for early syphilis were comparable to those obtained during weekly treatment with arsenical drugs, although with infections of longer duration there was apparently some retardation in the rate of fall of serum reagin after the use of penicillin. A linear relationship between duration of infection and rate of fall of reagin was shown. A study of the serologic response in terms of age, race and sex demonstrated in this material a delayed serologic response in Negro females and in patients under 20 years of age. Evidence is presented that the retarded response observed in these groups is related to the higher percentage of patients who had (a) longer duration of disease, (b) less efficacious treatment schedules or (c) a high incidence of recurrent lesions or to a combination of these factors.

The serologic response of the blood appeared to be independent of the presence or absence of abnormalities in the cerebrospinal fluid. The importance of the several factors which influence results in comparative serologic studies of this kind is discussed. These include: (1) the statistical method of analysis; (2) variations in sensitivity of the serologic tests used, and (3) differences in methods of reporting quantitative results and in defining the end point in quantitative technics.

182. Hazel, O. G.: Considerations with Respect to the Application in Private Practice of Penicillin Therapy for Early Syphilis, *J. Ven. Dis. Inform.* **28**:103 (June) 1947.

183. Clark, E. G.; Maxwell, R. W., and Scott, V.: The Serologic Response Following Penicillin Therapy for Early Syphilis, *Am. J. M. Sc.* **213**:535 (May) 1947.

with 4,800,000 units of penicillin in beeswax and peanut oil given over a period of eight days. Two treatment schedules were utilized: one group received two injections of 300,000 units daily; the other, one injection of 600,000 units daily. In their experience there appeared to be no advantage in giving more than one daily injection of penicillin-oil-beeswax. They attribute approximately 40 per cent of their treatment failures to reinfection rather than to relapse.

6. Penicillin alone versus penicillin combined with metal chemotherapy or fever therapy. Since the demonstration of Eagle and his co-workers¹⁷⁵ of a synergistic action between penicillin and oxophenarsine hydrochloride in experimental rabbit syphilis, many different schedules combining penicillin and heavy metals have been used in man.

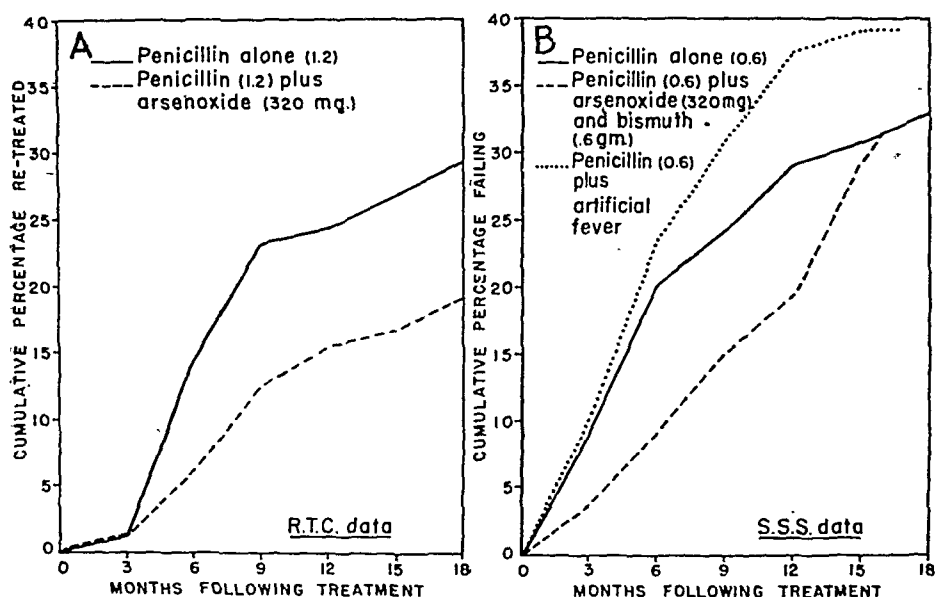


Fig. 4.—Comparison between penicillin alone and penicillin plus metal chemotherapy or fever therapy. *A*, cumulative percentage of patients retreated (data from rapid treatment centers); *B*, cumulative failure rates (Syphilis Study Section data).

The reports currently available are discrepant. The data from the rapid treatment centers suggest that the addition of oxophenarsine hydrochloride to aqueous solution of penicillin significantly reduces the percentage of patients who have to be retreated (fig. 4 *A*). Superiority of the combined penicillin oxophenarsine hydrochloride also was apparent early in the course of the work of the Syphilis Study Section, but with more prolonged follow-up observation the advantage was not maintained (fig. 4 *B*).

From neither study does there appear to be any virtue in short term courses of penicillin used in conjunction with artificial fever therapy,

175. Eagle, H.; Magnuson, H. J., and Fleischman, R.: The Synergistic Action of Penicillin and Mapharsen (Oxophenarsine Hydrochloride) in the Treatment of Experimental Syphilis, *J. Ven. Dis. Inform.* **27:3** (Jan.) 1946.

continue to have gradually decreasing titers over years require no treatment.

Penicillin in Late Syphilis.—Penicillin in Benign Late Syphilis: That visceal (hepatic) gummas heal promptly under therapy with penicillin has been demonstrated by Tucker and Dexter.¹⁸⁷ Two patients are reported who received a total dose of 920,000 and 3,200,000 units of penicillin respectively, with dramatic alleviation of the acute symptoms and sustained subjective and objective improvement over observation periods of six hundred and eighty-six and four hundred and ninety-one days respectively. In neither case was a therapeutic paradox observed. These data suggest that penicillin is at least as effective in the treatment of visceral gummas as other forms of antisyphilitic treatment and offers the additional advantage of almost complete lack of toxicity, a factor of some importance when disease of the liver is present.

Some of the problems arising in the treatment of syphilis with penicillin are described by Hill.¹⁸⁸ Of considerable interest is the fact that this author has had the opportunity of examining "a patient with an extensive destructive gumma involving the center of the face, including the nasal septum, and the hard palate, who had received 2,400,000 Oxford units of penicillin before admission, without improvement. Therapy with induced malaria completely resolved the lesion." This is the first report of "resistance" to penicillin in benign late syphilis.

Penicillin in Cardiovascular Syphilis: Most syphilologists agree that specific therapy in cardiovascular syphilis favorably influences the course of the disease and increases life expectancy. The efficacy of penicillin in this condition cannot yet be assessed, since the drug has been used for far too short a period.

Russek and his associates¹⁸⁹ have treated 15 patients with cardiovascular syphilis, including 4 with aortic aneurysm, with penicillin in relatively large doses (40,000 units every two hours). Significant untoward reactions necessitating discontinuance of the use of the drug were not encountered. The rarity of Jarisch-Herxheimer reactions in cardiovascular syphilis was strikingly in contrast to their frequency among patients with early syphilis similarly treated. Four of the 15 patients in the present series showed distinct improvement in coronary reserve after treatment. The authors conclude that harmful reactions

187. Tucker, H. A., and Dexter, D. D.: Treatment of Gummatous Hepatic Syphilis with Penicillin, *Arch. Int. Med.* **78**:313 (Sept.) 1946.

188. Hill, W. R.: Problems Arising in the Treatment of Syphilis with Penicillin, *New England J. Med.* **235**:919 (Dec. 26) 1946.

189. Russek, H. I.; Cutler, J. C.; Fromer, S. A., and Zohman, B. L.: Treatment of Cardiovascular Syphilis with Penicillin, *Ann. Int. Med.* **25**:957 (Dec.) 1946.

with penicillin sodium and 1 death for every 12,400 patients given it with penicillin-oil-beeswax. Hemorrhagic encephalitis was the principal cause of death.

Some French syphilotherapists have long divided the treatment of early syphilis into two phases: a "treatment of attack" and a "treatment of consolidation." Several have recently endorsed the use of penicillin as a satisfactory method of attack, but they are for the most part reluctant to dispense with follow-up metal chemotherapy to consolidate the early spirocheticidal effects of penicillin. The recently expressed ideas of Huriez and Desurmont¹⁷⁷ and of Barker Beeson¹⁷⁸ are an example of this.

Merklen and Vermeil¹⁷⁹ suggest that it is illogical to use penicillin alone in early syphilis. They recommend that antisyphilitic therapy be started with penicillin because of its prompt treponemicidal action and

TABLE 3.—*Severe Reactions and Deaths Reported by Thirty-Six Rapid Treatment Centers from July 1946 Through March 1947*

Type of Treatment	Total Patients Treated	Severe Reactions		Number of Deaths from Treatment
		No.	Rate per Thousand	
Aqueous solution of penicillin.....	12,157	104	8.6	0
Penicillin-oil-beeswax.....	4,106	21	5.1	0
Aqueous solution of penicillin with oxophenarsine hydrochloride.....	57,200	912	15.9	10
Penicillin-oil-beeswax with oxophenarsine hydrochloride.....	12,425	167	13.4	1
Total.....	85,888	1,204	14.0	11

because of its curative action against concomitant gonococcic infections and that this be followed by the use of arsenicals and bismuth. Having employed this schedule of therapy in a limited number of patients, Merklen and Nezelof¹⁸⁰ report that their early results have been entirely satisfactory.

In a small series of 17 patients Levaditi and Vaisman¹⁸¹ found a combination of penicillin and bismuth a satisfactory treatment of early

177. Huriez, C., and Desurmont, M.: Les pénicillo-chimothérapies d'assaut de la syphilis récente, *Presse méd.* **35**:401 (June 14) 1947.

178. Barker Beeson, M. B.: La penicilline dans le traitement de la syphilis, *Ann. de dermat. et syph.* **8**:395 (July-Aug.) 1946.

179. Merklen, F. P., and Vermeil, G.: Traitement antisyphilitique d'attaque et de blanchiment rapide pénicillino-arsenical, *Paris méd.* **37**:54 (Feb. 1) 1947.

180. Merklen, F. P., and Nezelof, C.: Essai de traitement accéléré de la syphilis: Assaut massif arsenico-bismuthique associé a des doses reduites de pénicilline, *Paris méd.* **37**:119 (March 8) 1947.

181. Levaditi, C., and Vaisman, A.: Traitement de la syphilis par une association liposoluble de bismuth et d'ester méthylique de pénicilline, *Presse méd.* **57**:781 (Nov. 23) 1946.

cerebrospinal fluid and on certain of the clinical manifestations of late neurosyphilis. They have treated with penicillin alone 111 patients with various forms of neurosyphilis. In 6 of 11 with dementia paralytica there were satisfactory remissions that have been sustained approximately two years. Forty-one patients with tabes dorsalis complained of a total of fifty-seven symptoms, subjective improvement in thirty-three of which was reported after penicillin therapy. There was no demonstrable correlation between the degree of abnormality of the cerebrospinal fluid and the symptomatic improvement. In a small number of patients with various clinical forms of meningovascular neurosyphilis the therapeutic results after penicillin were comparable to those usually observed after arsenotherapy. Striking improvement in the abnormalities present in the cerebrospinal fluid occurred both in patients with symptomatic and in those with asymptomatic neurosyphilis. The degree and rate of improvement were comparable to those previously observed after the use of fever therapy supplemented with metal chemotherapy. On the basis of their results, these authors state the belief that "the efficacy of the treatment is sufficiently close to the efficacy of fever to justify a trial of penicillin as the sole antisypilitic therapy for patients with asymptomatic neurosyphilis, tabes dorsalis, and the various manifestations of meningovascular neurosyphilis." In dementia paralytica they also believe it justifiable to use penicillin first, giving additional treatment, preferably the induction of fever, promptly if significant improvement in the clinical signs and in the cerebrospinal fluid fails to appear within three months.

Heyman¹⁹² has treated 141 patients with syphilis of the central nervous system with penicillin. His results are in general comparable to those reported by others. With the administration of 4,000,000 units of penicillin, "arrest" of the neurosyphilitic process was obtained in approximately 85 per cent of the cases. It is his belief that patients with early neurosyphilis respond more satisfactorily to penicillin than those whose disease is of longer standing, that the results in patients with maximal abnormalities of the cerebrospinal fluid in late syphilis are less satisfactory than the results in those with less significant abnormalities and that the early response of the spinal fluid is as good as that obtained from fever therapy with typhoid vaccine. Heyman recommends penicillin for the treatment of early neurosyphilis and late asymptomatic neurosyphilis provided adequate facilities for follow-up are available. He regards fever therapy as the treatment of choice in late asymptomatic neurosyphilis.

192. Heyman, A.: The Treatment of Syphilis of the Central Nervous System with Penicillin, *Am. J. M. Sc.* **213**:661 (June) 1947.

Maillard and Orzel¹⁸⁴ have employed quantitative complement fixation tests in the study of 693 patients with early syphilis who received treatment with penicillin. These authors, finding significantly higher titers in patients with secondary syphilis than in those in the primary stage of the disease, express their belief that quantitative tests are of considerable value in estimating the probable duration of a recently acquired infection. They stress the even greater value of quantitative serologic tests in determining the effectiveness of treatment of early syphilis, noting that in their group of patients serologic relapse usually coincided with the reappearance of infectious mucocutaneous lesions.

Heggie and his co-workers¹⁸⁵ believe that flocculation tests and complement fixation tests should be performed routinely in parallel, and they emphasize the fact that since the introduction of penicillin therapy this routine parallel testing is more than ever necessary. If only one test can be undertaken, then it is believed that a flocculation test should be used.

Thomas¹⁸⁶ has recorded certain observations on the clinical significance of quantitative serologic tests for syphilis. He believes that "patients with negative spinal fluid findings but persistently low blood STS titers of less than 10 (units) for more than one year after rapid treatment for primary or secondary syphilis require no further therapy unless marked rises in STS titer occur." Patients treated for primary or secondary syphilis who continue to have positive reactions to serologic tests in high titer should in his opinion be retreated, but he cautions that the physician should not expect rapid drops in the titers of such patients after retreatment. Most patients given rapid treatment for early latent syphilis of less than six months' duration became seronegative within one year after treatment. The persistence of low titers in such patients for more than one year is not, he thinks, an indication for further treatment. The longer the duration of the latent syphilitic infection, the longer was the time required for the reactions to blood tests to become negative. The aim of treatment in late latent or late symptomatic syphilis is primarily to prevent further progress of the disease. Thomas expresses the belief that if notable sustained rises in titer occur further treatment is indicated but that patients who

184. Maillard, E. R., and Orzel, A.: The Value of the Quantitatively Standardized Complement Fixation Test in the Diagnosis and Treatment of Early Syphilis, *Am. J. Syph., Gonorr. & Ven. Dis.* **30**:490 (Sept.) 1946.

185. Heggie, J. F.; Maguire, J. C.; Bull, M. M., and Heggie, R. M.: Results of Parallel Kahn and Wassermann Tests in Relation to Penicillin Therapy of Syphilis, *Lancet* **1**:588 (May 3) 1947.

186. Thomas, E. W.: The Clinical Significance of the Quantitative Serologic Tests for Syphilis, *Am. J. Syph., Gonorr. & Ven. Dis.* **30**:317 (July) 1946.

concurrently with malarial therapy resulted in clinical improvement in at least 10 of 17 patients (58 per cent). Improvement in the abnormalities of the spinal fluid was even more complete than when penicillin alone was given. There were no cases in which either the cell count or the total protein in the cerebrospinal fluid was abnormal for a period in excess of twenty weeks after therapy.

The effectiveness of concurrent penicillin-malaria therapy was such as to make it, in these authors' opinion, the treatment of choice for patients with dementia paralytica.

Seven patients with dementia paralytica were treated by Smith¹⁹⁵ with intramuscularly administered penicillin. No penicillin was found in the spinal fluid with the dosage employed. Of these patients, 4 made a "social recovery," 1 was improved, 1 was not improved and 1 died. Studies of the spinal fluid revealed improvements in both cell count and protein content; the reactions to colloidal gold and Wassermann tests remained abnormal longer.

Rose and Solomon¹⁹⁶ have utilized penicillin in a unique manner, namely, in combination with approximately one half the amount of fever therapy usually considered optimal. The clinical results in the first 100 patients who have been under observation for at least a year after this and other forms of therapy are described. The majority (75 per cent) of these patients had dementia paralytica. Fifty-two (69 per cent) were improved, 21 had shown no change and 2 were worse.

Penicillin in Abnormalities of the Cerebrospinal Fluid: The over-all early effects of administration of penicillin on the abnormalities of the cerebrospinal fluid in cases of symptomatic neurosyphilis have been described by Reynolds.¹⁹⁷ A total of 149 patients with various manifestations of late neurosyphilis (including tabes dorsalis, dementia paralytica, primary optic atrophy, meningovascular neurosyphilis and Erb's syphilitic spastic paraplegia) were treated with penicillin or with penicillin used in combination with malarial therapy. Improvement in the spinal fluid generally was apparent. As a rule, the cell count and protein content promptly became normal and remained so. The condition as revealed by the reactions to colloidal gold, mastic and Wassermann tests more gradually improved, the improvement usually being well sustained. The degree and rapidity of improvement in these patients with such diverse

195. Smith, R. H. F.: General Paresis of the Insane Treated with Penicillin, *Lancet* 1:665 (May 17) 1947.

196. Rose, A. S., and Solomon, H. C.: Penicillin in the Treatment of Neurosyphilis: A Study of One Hundred Cases Followed Twelve Months or More, *J. A. M. A.* 133:4 (Jan. 4) 1947.

197. Reynolds, F. W.: Penicillin in the Treatment of Neurosyphilis: IV. Cerebrospinal Fluid Changes in Cases of Symptomatic Neurosyphilis, *Ann. Int. Med.* 26:393 (March) 1947.

to penicillin are uncommon in cardiovascular syphilis during the treatment in early post-treatment periods and that this form of therapy warrants further evaluation.

Penicillin in Neurosyphilis: Gammon, Stokes and their collaborators¹⁹⁰ report strikingly good results from therapy with penicillin alone in neurosyphilis and consider this "the first choice for the first treatment of neurosyphilis."

Their analysis of 161 patients with various manifestations of syphilis of the central nervous system indicates that the greatest effect on symptoms and signs occurred with respect to the psychoses, the incoordination, the tremors and the speech defects of dementia paralytica and the lightning pains of tabes dorsalis. Abnormalities of the spinal fluid responded dramatically. Within two years the spinal fluid in 62 per cent of their patients was normal or "near normal." In all types of neurosyphilis the outstanding therapeutic response was again in weight, usually accompanied with a sense of increased well-being.

In dementia paralytica, mental symptoms improved in 72 per cent of 47 patients, the most notable results being observed in those with severe symptoms of short duration. In juvenile paresis, improved mental status was noted less frequently. There were 40 patients with tabes or the tabetic form of dementia paralytica with lightning pains, and of these, 33 (82 per cent) were "improved." In the relief of tabetic pain, these authors believe that the effects of penicillin are "greater than might be expected as a result of spontaneous remission and on the whole compare favorably with results of other forms of therapy." In other symptoms of tabes no striking changes were noted. In meningovascular and asymptomatic neurosyphilis, the results were measured by the response of the spinal fluid. Fourteen patients had convulsions, a symptom which failed to improve notably after penicillin therapy.

The occurrence of neural Herxheimer reactions is recorded. Transient increases in mental abnormalities developed in 5 parietic patients; 4 with tabes dorsalis had exacerbation of their pains, and in 2 with syphilis of the spinal cord there developed transverse myelitis.

Koteen, Doty, Webster and McDermott¹⁹¹ express the belief that "the penicillin therapy of neurosyphilis (exclusive of primary optic atrophy) approaches and may equal fever therapy in effectiveness." These investigators found that the administration of penicillin over a two week period produced a striking effect on abnormalities of the

190. Gammon, G. D.; Stokes, J. H., and others: Penicillin Therapy Alone in Neurosyphilis: An Analysis of Clinical Results, *Ann. Int. Med.* **25**:412 (Sept.) 1946.

191. Koteen, H.; Doty, E. J.; Webster, B., and McDermott, W.: Penicillin Therapy in Neurosyphilis, *Am. J. Syph., Gonorr. & Ven. Dis.* **31**:1 (Jan.) 1947.

Among a group of 730 patients with early syphilis treated with penicillin by Cole and his co-workers²⁰⁰ there were 47 pregnant women. These authors concur in the belief that syphilis in pregnancy is an ideal situation in which to use penicillin because of the absence of severe reactions and because the drug may be used successfully even late in pregnancy provided the child is still viable. In their experience, there appeared to be no great danger of miscarriage or premature delivery, no evidence of damage to the unborn child, or, in contrast to intensive arsenotherapy, no danger of hemorrhagic encephalitis in the mother. Moreover, penicillin proved efficacious even when administered late in the course of pregnancy. There was 1 child with congenital syphilis, born of a mother who had received a total of but 300,000 units over a period of seven and one-half days (5,000 units every three hours). One other pregnancy terminated in stillbirth of a macerated fetus of 7 months, and although there were no clinical evidences of syphilis the authors interpret this as a therapeutic failure. There were two premature births, which are not attributed to penicillin therapy; in neither of the 2 children was syphilis known to develop. The authors stress the necessity of frequently repeated quantitative serologic tests in the management of the pregnant syphilitic woman and of her child.

Speiser and his co-workers²⁰¹ delineate the ideal form of anti-syphilitic therapy in the pregnant woman as one which involves (1) freedom from serious toxic effects, (2) prevention of prenatal syphilis, (3) cure of the maternal infection, (4) cure of the congenitally syphilitic child in utero and (5) the completion of therapy within a short period. In their opinion, penicillin fulfils these requirements better than any drug previously employed. Among a series of two hundred and sixty-one pregnancies in 259 women, syphilis was proved to have developed in only 1.5 per cent of the infants. It is noted that prenatal syphilis may be prevented regardless of the period of gestation in which penicillin is started, that frequent observations of the mother during pregnancy are essential, that if a maternal clinical or serologic relapse occurs during the prenatal period retreatment may assure a nonsyphilitic child and that a patient who has responded satisfactorily after previous penicillin therapy need not be treated during a subsequent pregnancy provided adequate follow-up observations are assured.

From their studies involving three schedules of intensive antisiphilitic therapy in the prevention of prenatal syphilis, Olansky and Beck²⁰²

200. Cole, H. N.; Ayres, S., III; Barr, J. H.; Genatios, R.; Held, B.; Murphy, W. W.; Printz, D. R., and Strauch, J.: Use of Penicillin in the Treatment of Syphilis in Pregnancy, *Arch. Dermat. & Syph.* **54**:255 (Sept.) 1946.

201. Speiser, M.; Flaum, G.; Moon-Adams, D., and Thomas, E. W.: Penicillin Therapy for Syphilis in Pregnancy, *J. Ven. Dis. Inform.* **28**:108 (June) 1947.

202. Olansky, S., and Beck, R.: Rapid Treatment of Prenatal Syphilis, *Am. J. Syph., Gonorr. & Ven. Dis.* **31**:51 (Jan.) 1947.

Penicillin in Asymptomatic Neurosyphilis: Moore and Mohr¹⁹³ have presented the detailed results of penicillin therapy in 48 patients with early asymptomatic neurosyphilis and in 43 with late asymptomatic neurosyphilis followed for more than three months after treatment. Pointing out that there are no valid data available on which to base a comparison with the results from no treatment whatsoever or from any previously available form of therapy, the authors state:

At the moment, the most that can be said is that penicillin exerts a profoundly favorable effect on spinal fluid abnormalities in early and late asymptomatic neurosyphilis; that this effect is manifest, in order of promptitude and extent, on cell count, protein content, colloidal test, and, last of all, on the complement fixation (Wassermann) reaction; and that the speed and extent of the disappearance of all spinal fluid abnormalities is dependent upon the two factors of degree of these abnormalities before treatment and of the duration of syphilitic infection. Within the brief time limit of this study, and keeping in mind the small number of cases involved, spinal fluid normality, once achieved, seems usually to be stable.

They consider that in either early or late asymptomatic neurosyphilis the reappearance of increased cell count, increased protein or both is an indication for retreatment. They also suggest that it may be desirable to retreat patients in whom the Wassermann reaction of the spinal fluid remains positive, with little change from its original titer, for a year after the first course of penicillin therapy. Their personal preference for retreatment is the induction of fever and malaria in combination with the administration of penicillin.

Penicillin in Dementia Paralytica: Reynolds, Mohr and Moore¹⁹⁴ concur that in the treatment of dementia paralytica penicillin gives promise of becoming a valuable therapeutic adjunct. In their experience, however, the concurrent use of penicillin and malaria was productive of significantly better results than the use of penicillin alone. Forty-one patients with dementia paralytica were treated at the Johns Hopkins Hospital with commercial penicillin; 24 were treated with penicillin alone and 17 with penicillin and malarial therapy. Penicillin alone, in doses ranging from 2,000,000 to 10,000,000 units, produced at least some degree of clinical improvement in 11 of 24 patients (46 per cent). The response was better among patients whose symptoms were of recent onset. No patient whose symptoms had been present for a year or more prior to the institution of penicillin treatment showed any clinical improvement. Improvement in the abnormalities of the spinal fluid generally was apparent, although 3 patients showed persistent evidence of cerebrospinal fluid "activity." Penicillin administered

193. Moore, J. E., and Mohr, C. F.: Penicillin in the Treatment of Neurosyphilis: I. Asymptomatic Neurosyphilis, *Am. J. Syph., Gonorr. & Ven. Dis.* **30**: 405 (Sept.) 1946.

194. Reynolds, F. W.; Mohr, C. F., and Moore, J. E.: Penicillin in the Treatment of Neurosyphilis: II. Dementia Paralytica, *J. A. M. A.* **131**:1255 (Aug. 17) 1946.

syphilis and in early neurosyphilis, penicillin appeared of little or no value in the treatment of the late manifestations of the disease.

Rose, György and Ingraham²⁰⁴ report that further experience with penicillin in the treatment of syphilitic infants confirms their earlier impression that penicillin sodium given by repeated intramuscular injections is a satisfactory therapy for the congenitally infected syphilitic infant. They now have treated 36 infants with congenital syphilis with intramuscular injections of penicillin in doses ranging from 11,000 to 75,000 units per pound of body weight over periods of seven to fifteen days. Nineteen have become clinically well and seronegative, 6 have become clinically well but remain seropositive and 3 were still seropositive when the follow-up study was interrupted. Two were clinically well but had doubtful reactions to serologic tests for syphilis, 7 died, none as a direct result of penicillin therapy, and 4 have been treated too recently to evaluate beyond the prompt clinical improvement. There was no instance of serologic relapse and only one clinical relapse. These authors recommended that the total dosage of penicillin sodium be not less than 75,000 units per pound of body weight and that the course of therapy be not less than fifteen days. They find no necessity for low initial dosage and recommend early hospitalization, with vigilant pediatric supervision.

Observations incident to the treatment of 252 infants with early congenital syphilis by the use of penicillin have been recorded by Platou and his co-workers, representing five cooperating university clinics.²⁰⁵ A single course of penicillin administered over a period of seven and one-half to fifteen days yielded satisfactory results in 73 per cent of the infants and unsatisfactory results in 9.1 per cent, while in 17.9 per cent the results are classified as uncertain. Dosage schedules employing more than 40,000 units of the drug per kilogram of body weight yielded better results than those utilizing lesser amounts. Most babies became seronegative between the fourth and twelfth months after therapy, but serologic reversal was not unusual after this period had elapsed. It is recommended that infants with syphilis be given a total dosage of at least 100,000 units per kilogram of body weight and that this amount be divided into approximately one hundred and twenty intramuscular injections, given every three hours over a period of twelve to fifteen days.

204. Rose, E. K.; György, P., and Ingraham, N. R., Jr.: Penicillin in the Treatment of the Syphilitic Infant: A Progress Report, *J. Pediat.* **29**:567 (Nov.) 1946.

205. Platou, R. V.; Hill, A. J., Jr.; Ingraham, N. R.; Goodwin, M. S.; Wilkinson, E. E.; Hansen, A. E., and Heyman, A.: Early Congenital Syphilis: Treatment of Two Hundred and Fifty-Two Patients with Penicillin, *J. A. M. A.* **133**:10 (Jan. 4) 1947.

manifestations of neurosyphilis could not definitely be correlated with the penicillin dosage, the duration of symptoms, or the extent of the abnormalities of the spinal fluid. The results following therapy with penicillin plus malaria were more favorable than those following treatment with penicillin alone.

Neural Reactions of the Jarisch-Herxheimer Type.—Reviewing the records of 208 patients with various forms of neurosyphilis treated with penicillin, Tucker and Robinson¹⁹⁸ report that some reaction to the initiation of treatment occurred in 54 patients (26 per cent). The majority of these reactions were febrile, but transitory mental confusion or agitation also occurred. In 2 patients receiving penicillin for dementia paralytica hallucinatory and paranoid trends became so extreme that it became necessary to commit both to institutional care. These authors report 2 additional patients with neurosyphilis in whom convulsions developed early in the course of penicillin therapy. The occurrence of these reactions within the first forty-eight hours of penicillin therapy and their association with a febrile response suggest that they were reactions of the Jarisch-Herxheimer type. It seems unlikely that they were due to a direct irritative action of penicillin, since the symptoms subsided spontaneously despite the fact that penicillin therapy was continued in undiminished doses.

Penicillin in Prenatal Syphilis.—In a study to determine whether penicillin crosses the placental barrier early in pregnancy, Woltz and Wiley¹⁹⁹ administered the drug preoperatively to 6 women for whom interruption of pregnancy was advised for therapeutic reasons. Penicillin was given either intravenously or intramuscularly, and at the time of operation specimens of maternal blood, amniotic fluid and fetal blood or tissue fluid were obtained. Their data reveal that (1) penicillin was found in the 10, 20, 21 and 25 week fetuses and that (2) penicillin was present in the amniotic fluid of the 12 week fetus after the administration of only 35,000 units to the mother.

Since arsenical drugs do not pass in high concentration to the fetal tissues prior to the latter half of pregnancy, the authors imply that penicillin may be the drug of choice in the prevention of congenital syphilis, especially when therapy is begun in early pregnancy.

198. Tucker, H. A., and Robinson, R. C. V.: Neurosyphilitic Patients Treated with Penicillin: Probable Herxheimer Reactions, J. A. M. A. **132**:281 (Oct. 5) 1946.

199. Woltz, J. H. E., and Wiley, M. M.: The Transmission of Penicillin to the Previsible Fetus: Its Significance in Prenatal Syphilis, J. A. M. A. **131**:969 (July 20) 1946.

Book Reviews

Heparin in the Treatment of Thrombosis. By J. Erik Jorpes. Second edition. Price, \$6.50. Pp. 260, with 21 illustrations, 2 in color. New York: Oxford University Press, 1947.

This monograph presents the results of a comprehensive study of the anti-coagulants, emphasizing their development, chemistry and clinical uses. It is written by a member of the Swedish school who is particularly interested in and has done much to develop heparin as a clinical agent and is, to that extent, biased.

The chemical researches which are necessarily included for the sake of completeness are perhaps too technical for the average physician but serve nicely to illustrate the methods of research necessary to isolate and define compounds of therapeutic value. This would seem to be timely in view of the increasing number and importance of specific chemical agents.

The clinical efficacy of heparin has been thoroughly evaluated in a large series of cases. Results, which seem to be valid, are certainly exciting and warrant much more clinical trial. Several important points are brought out which have not been emphasized in our literature. For example, there is the claim, on apparently good clinical basis, that heparin is useful therapeutically in thromboembolic states for its thrombolytic action as well as useful prophylactically. The author suggests the use of the drug over long periods of time, with gradually decreasing dosage as improvement progresses, and many failures have been attributed to the sudden and premature cessation of therapy. It is interesting to find that in large autopsy series thromboembolic phenomena are at least as common in medical cases as they are in surgical cases.

Dangers of the use of heparin are minimized, and the intravenous use of protamine sulfate for the instantaneous reversal of its action is emphasized.

The author discusses "dicumarol," apparently only to condemn its use. The objection to this drug and the firm stand for heparin have much basis in fact, but further trial and more clinical experience seem necessary before one may pass on the relative merits of the two drugs. The statement in the preface that "heparin is as specific in thrombosis as insulin is in diabetes" may not be entirely correct, but the subject certainly shows a great deal of promise.

This volume constitutes an excellent introduction for the discriminating reader.

Cushny's Pharmacology and Therapeutics. Revised by Arthur Grollman and Donald Slaughter. Thirteenth edition. Price, \$8.50. Pp. 868, with 74 illustrations. Philadelphia: Lea & Febiger, 1947.

In its present form, this standard work, now in its thirteenth edition, continues to justify its reputation as a ". . . severely critical, rigorously scientific, general textbook written by an experimental pharmacologist." To this statement it should be added that the present editors contribute to the background of the book the further qualifications of a well known pharmacologist and internist.

More specifically, this book is recommended especially by its combination of reasonable size with completeness; it never leads the reader into purely speculative matters, and yet the entire field of modern pharmacology is amply covered. Emphasis is placed on the practical application of the subject to practical therapeu-

deduce that intensive treatment offers the best outlook for a nonsyphilitic child. One hundred and forty-seven patients were treated, 74 by five or seven day schedules of arsenobismuth therapy, 24 by the use of penicillin alone and 49 with combinations of oxophenarsine hydrochloride, bismuth and penicillin. The pregnancies resulted in 128 live births. Eleven terminated in abortions or stillbirths, an incidence considered to be no greater than that in a similar, nonsyphilitic group. Nine of the patients became pregnant again but received no antisymphilitic therapy during the second pregnancy. Despite the fact that 64 of the women were treated during the last trimester of pregnancy, syphilis developed in only 1 infant; the mother had been treated with penicillin and metal chemotherapy. The incidence of untoward reactions with all three regimens was low, particularly with the schedules employing penicillin alone and penicillin oxophenarsine hydrochloride and bismuth in combination. The authors stress that quantitative serologic tests for syphilis and careful physical examinations be performed monthly during pregnancy so that in the event of reinfection or relapse retreatment may be instituted in time to prevent congenital syphilis.

Penicillin in the Treatment of Syphilis in Children.—Yampolsky and Heyman²⁰³ have used penicillin in the treatment of 61 children with various manifestations of syphilis. Included in their series were 32 infants, and satisfactory results were obtained in 23 of them. An immediate clinical response was observed in all patients, and healing of cutaneous and mucosal lesions often occurred by the end of the course of treatment. Osseous lesions also showed prompt improvement, but complete resolution usually did not occur for two or three months. Of 9 patients in whom treatment was considered to have failed, there were 4 clinically well but seroresistant, 2 clinically worse with associated serologic relapses and 3 who died. None of the deaths was thought to be due to penicillin.

The majority of patients with interstitial keratitis did not improve satisfactorily with parenterally administered penicillin, which also was of little value in the treatment of Clutton's arthritis. The changes in the cerebrospinal fluid in late congenital asymptomatic neurosyphilis were in general satisfactory and comparable to those obtained with fever therapy. Little or no clinical improvement was noted in juvenile paresis treated with penicillin. One patient with mild nerve deafness had improved hearing, and another with severe deafness showed no improvement after receiving penicillin therapy.

In general, the results obtained with penicillin in the treatment of syphilis in children seemed to depend on the nature and duration of the disease. Although effective in the treatment of infantile congenital

203. Yampolsky, J., and Heyman, A.: Penicillin in the Treatment of Syphilis in Children, J. A. M. A. **132**:368 (Oct. 19) 1946.

and procedures which have proved of greatest use in meeting these situations. The style of presentation and the practical manner in which the subject is handled make the book especially valuable to public health engineers and sanitarians in their work in the field.

The first part is devoted to various aspects of milk sanitation. In this section one finds excellent discussions on the essentials of the sanitary production of milk and on many of the problems connected with pasteurization. Attention is also given to laboratory procedures used to evaluate a milk supply and the sanitary control of frozen dessert. The chapter dealing with the planning and administering of a milk control program is full of useful suggestions for any one interested in the field of public health administration.

Problems of food sanitation and control are discussed in the second section. Following the trend of modern concepts of public health, the author emphasizes the educational approach in coping with problems of food handlers.

The usefulness of this book is enhanced by a number of appropriate appendixes, which contain a wealth of practical information pertinent to the field activities of personnel dealing with milk and food sanitation. The simple style and presentation make it a valuable reference for any one interested.

Paravertebral Block in Diagnosis, Prognosis and Therapy. By Felix Mandl, M.D. Translated by Gertrude Kallner. Price, \$6.50. New York: Grune & Stratton, Inc., 1947.

Paravertebral block used to be thought of as belonging to the domain of the vascular surgeon, who would use it as a preoperative test for sympathectomies or employ it for the relief of vasospastic disturbance occurring during the acute vascular occlusions. Professor Mandl has long been a student in this field; in fact, he published a little known monograph on this subject twenty-five years ago. The present volume is a greatly extended body of observations, gathered under difficult conditions in Vienna and later in Jerusalem.

The internist will be greatly interested in the use of this method as a differential diagnostic procedure in painful visceral conditions. More than that, the method has therapeutic value, since single or repeated injections of procaine hydrochloride into the appropriate sympathetic ganglions are described to have value. The chapters on the results of paravertebral injections in angina pectoris, paroxysmal tachycardia and essential hypertension are especially stimulating.

This is a valuable contribution on temporary block of the sympathetic ganglions. There is no field of medicine in which it could not be profitably applied. The translation is smooth and rapidly understood but needs more close editing. The illustrations are simple and diagrammatic.

Significance of the Extracellular Fluid in Clinical Medicine. By L. H. Newburgh, M.D. Price, \$1.80. Pp. 64. Ann Arbor, Mich.: J. W. Edwards, Inc., 1946.

The author of this monograph is well qualified to write on the significance of extracellular fluids in clinical medicine, as he has spent many years investigating certain phases of the subject. He has accomplished the difficult task of translating information of a highly technical nature into language understood by most clinicians.

The first part of the monograph is taken up with the physiology of extracellular fluids, and the nature of the regulatory mechanisms is outlined in a simple but emphatic manner. The second portion is concerned with the clinical significance of the abnormalities which occur in the extracellular fluid system. The author first familiarizes the reader with the features of the extracellular fluid in its normal

Further observations on the use of penicillin in the treatment of infantile congenital syphilis have been reported by the university groups at New Orleans, Philadelphia, Baltimore and Galveston.²⁰⁶ Reactions in children to penicillin therapy have been inconsequential, and deaths occurring among the combined series of 191 infants could in no instance be related to the use of penicillin. The percentage of treated infants in whom seronegativity developed increased with each month of observation for at least eighteen months.

Wyvell,²⁰⁷ reporting the results of penicillin treatment of 40 patients with congenital syphilis, finds the drug valuable in neonatal syphilis and in syphilis acquired in childhood. Her results with congenital syphilis in older children were less favorable; in 7 who had involvement of the central nervous system the outcome was "not very encouraging."

Hill, Platou and Komentani²⁰⁸ properly point out that until the spontaneous evolution of a self-limited process is known it is impossible to assess the worth of any form of therapy intended to ameliorate the process. They have considered osseous congenital syphilis in relation to the effects of penicillin on the rate of healing in this light. These investigators' study indicates that:

1. The behavior of osseous congenital syphilis in untreated infants follows a fairly definite pattern of rapidly increasing severity during the first 3 months of life and slow healing thereafter. Improvement results from decreasing severity of osteomyelitis and osteochondritis; periosteal changes increase in prominence over a longer period and persist as the commonest residua. The course of a given lesion in any individual patient cannot be accurately predicted.

2. Dosages of penicillin employed so far have temporarily accelerated healing of osseous syphilis only in infants treated during the first three months of life. This acceleration, as in untreated controls, occurs principally in osteochondritis and osteomyelitis; simultaneous improvement in periostitis is only of probable significance. No such significant effects were observed among those treated during the next four months. The mode of healing for any particular type of lesion, as herein described, has not been evaluated.

3. Increase in severity of these lesions during or shortly after penicillin therapy occurs in an age group where this phenomenon is to be expected without treatment.

4. Pseudoparalysis disappears without any specific changes in the roentgenograms; indeed, osseous lesions may even appear worse after pseudo-paralysis subsides.

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(To Be Concluded)

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tics, a fact which should appeal to the busy physician as well as to the harassed medical student. No attempt is made to include the exhaustive detail of a compendium.

An introductory section of forty pages is valuable for its concise discussion of the principles of pharmacodynamics and of pharmacopeias and biologic assay. The body of the book considers in succession various groups of drugs which have been classified in the ways that have seemed most logical for each group. Thus, the inorganic substances are considered together, as are substances characterized chiefly by local action, those characterized by action after absorption, anthelmintics, antiseptics and disinfectants and vaccines, sérums and miscellaneous biologic preparations. Several drugs, such as the newer sulfonamide compounds, the antibiotics and folic acid, make their first appearance in a textbook of pharmacology.

An additional classification is appended which groups all the drugs previously considered according to their therapeutic uses and which would seem especially valuable from the purely practical standpoint.

Penicillin Therapy Including Streptomycin, Tyrothricin and Other Antibiotic Therapy. By John A. Kolmer, M.D. Second edition. Price, \$6.00. Pp. 339, with 27 illustrations. New York: D. Appleton-Century Company, Inc., 1947.

The appearance of the second edition of this book two years after that of the first is rather definite proof that there was need of such a textbook and that there is a real necessity to record promptly the newer studies of antibiotics, a subject which is going ahead by leaps and bounds. Because of all the new material that has appeared in the last two years, Kolmer has been obliged to rewrite completely the second edition. He has also incorporated a considerable number of additional illustrations. Even with the many changes that have been necessary to bring the new edition up to date at the time of publication, it is almost impossible really to keep a book au courant with the studies that are appearing almost daily in the field of antibiotic therapy. Bacitracin is an excellent example. Kolmer has two paragraphs on this particular new antibiotic substance, which gives promise of being extremely important in the future and which will require pages in the third edition of the book when and if it appears. A long chapter is devoted to penicillin in the treatment of syphilis, but little is said about the failure of this drug to be always satisfactory, probably because at the time of publication the reports of failure had not yet started to come in.

These criticisms are not truly critical but are made merely to illustrate the difficulties of keeping a book up to the minute on a subject which is so mutable. The advice and information that Kolmer gives on how properly to use antibiotics are excellent. The book may be used by physicians with the confidence that the information on what is known at the time of its appearance is authentic and detailed. It can be recommended highly to every type of specialist who is dealing with certain infections, from those of the eye to those of the genitals.

Milk and Food Sanitation Practice. By H. S. Adams, B.Sc. Price, \$3.25. New York: The Commonwealth Fund, 1947.

This book fills an important need in the field of public health by presenting in a clear and well organized manner the present concepts of the principles of milk and food sanitation and how these principles may be put into practice. The author points out the usual problems encountered in the field of milk and food sanitation and then proceeds to describe in concise and not too technical language the methods

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state and then discusses the relations between abnormalities of this fluid and a number of diseases.

After the reader understands the nature of the extracellular fluid and its regulation by the kidneys, he is prepared to evaluate the clinical significance of abnormalities in this system.

La réticulose histiomonocytaire. By P. Cazal. Price, 350 francs. Pp. 196. Paris: Masson & Cie. 1946.

This is an extremely difficult book to review. It is on a subject which is comparatively new. In the English language, the terminology employed by pathologists differs from person to person, and many of the papers written in English are difficult to understand for that reason. When a subject is written in French, it can be readily appreciated that the reader is going to have a great deal of trouble in interpreting the French nomenclature, translating it into English and then in turn transferring the English nouns to the terms that the pathologist is accustomed to use.

Undoubtedly the monograph will be of considerable value to one who is interested in the subject matter treated by Dr. Cazal, but most pathologists will probably find that the book is not of practical value to them, and clinicians will discover that they probably will not be able to make use of it at all.

Die hormonalen Aspekte des Fortpflanzungsprozesses. By Jules Samuels, M.D. Pp. 152. Amsterdam, Holland: Holdert & Company, 1947.

This monograph reviews present concepts of the interrelationship of various hormones in the process of fertilization. The gist of it is summarized in English, French and Dutch as well as German—a helpful gesture to those unfamiliar with the last language, which is used for the body of the text. An excellent bibliography appears at the end.

On the whole, the work is useful for reference. It will interest a limited number of readers. Students in the field, however, will appreciate the manner in which the author has brought together varying views on a complicated phase of endocrinology.

Health Instruction Yearbook, 1946. Compiled by Oliver E. Byrd. Price, \$3. Pp. 399. Stanford University, Calif.: Stanford University Press, 1946.

This fourth edition of the "Health Instruction Yearbook" is a summary complete with bibliographic references to three hundred and eighty-four of the most recent articles appearing in various scientific, medical, statistical and public health journals, including *The Journal of the American Medical Association* and the *American Journal of Public Health*.

It includes a new chapter on international health compatible with awakened American participation in world affairs and with the fact that major health problems are not restricted by geographic or international boundaries.

This book achieves its purpose well in that it contains a wealth of the latest and most reliable health facts essential to all public health personnel, educators, librarians and statisticians, as well as helping those interested to keep abreast of recent advances in the mounting mass of scientific literature. It does not contain the detailed medical information sought by practicing physicians or medical researchers.

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